QUEEN MARY, UNIVERSITY OF LONDON

Bayesian Network Decision-Support for Severe Lower Limb Trauma

Zane Brendan Perkins

Centre for Trauma Sciences
Blizard Institute
Queen Mary, University of London

2016

Submitted in partial fulfilment of the requirements of the degree of
Doctor of Philosophy

SUPERVISORS

Colonel Nigel Tai, QHS, MS, FRCS

Clinical Director, Trauma Services

The Royal London Hospital

London, UK

Senior Lecturer, Academic Department of Military Surgery and Trauma

Royal Centre for Defence Medicine

Birmingham, UK

Dr William Marsh, Ph.D.

Senior Lecturer, Risk and Information Research Group

School of Electronic Engineering and Computer Science

Queen Mary, University of London

London, UK

Professor Karim Brohi, FRCA, FRCS

Professor of Trauma Science

Centre for Trauma Science

The Blizard Institute

Queen Mary, University of London

London, UK

STATEMENT OF ORIGINALITY

I, Zane Brendan Perkins, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged.

I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material.

I accept that the College has the right to use plagiarism detection software to check the electronic version of the thesis.

I confirm that this thesis has not been previously submitted for the award of a degree by this or any other university.

Zane Brendan Perkins

1 September 2015

ASSOCIATED PUBLICATIONS

PUBLICATIONS

Perkins ZB, De'Ath HD, Sharp G, Tai NRM. Factors affecting outcome after traumatic limb amputation. *British Journal of Surgery.* 2012; 99(Suppl 1): 75–86.

Yet B, **Perkins Z**, Fenton N, Tai N, Marsh W. Not just data: A method for improving prediction with knowledge. *Journal of Biomedical Informatics.* 2014; 48: 28-37.

Yet B, **Perkins ZB**, Rasmussen TE, Tai NR, Marsh DW. Combining data and meta-analysis to build Bayesian networks for clinical decision support. *Journal of Biomedical Informatics.* 2014; 52: 373-85.

Yet B, **Perkins Z**, Tai N, Marsh W. Explicit evidence for prognostic Bayesian network models. *Studies in Health Technology and Informatics*. 2014; 205: 53-7.

Perkins ZB, Yet B, Glasgow S, Cole E, Marsh W, Brohi K, Rasmussen TE, Tai NR. Meta-analysis of prognostic factors for amputation following surgical repair of lower extremity vascular trauma. *British Journal of Surgery*. 2015; 102(5): 436-50.

ACKNOWLEDGEMENTS

I would like to thank a number of people who have helped make this thesis possible.

First, Colonel Nigel Tai for giving me the opportunity to undertake this research, for the confidence he has shown in me, and for his invaluable mentorship and supervision throughout.

Professor Karim Brohi and Dr William Marsh for their astute advice and helpful guidance.

Barbaros Yet for his friendship and the countless hours of discussion, collaboration, and deliberation.

The Academic Department of Military Surgery & Trauma (ADMST), the Royal Centre for Defence Medicine, for funding this research.

Professor Hermant Kocher and Mr Manoj Ramachandran for reviewing the progress of my thesis and offering their expertise and advice.

Professor Todd Rasmussen, Irma McNamee, Raul Corpus, and the United States Army Institute of Surgical Research for their hospitality, generosity, and collaboration.

My friends and colleagues at the Centre for Trauma Sciences: Simon Glasgow, Imran Raza, Sirat Khan, Ross Davenport, Henry De'ath, Jo Manson, Veena Naganathar, Elaine Cole, Karen Hoffman, Claire Rourke, Anita West, and Simon Eaglestone, who have all helped and inspired me greatly.

Finally, to my family and friends for their interest in my pursuits and encouragement along the way, and Ivana for her endless patience and support.

ABSTRACT

Severe lower limb injuries are potentially devastating and pose some of the most difficult decisions in trauma surgery. The goal is to ensure survival and reconstruct the most functional limb possible. Ideally this is achieved by salvaging the injured limb. However, in certain situations amputation is the safest and most effective method of achieving an optimal outcome. Errors in these decisions may have profound consequences, yet they are frequently based on incomplete information and uncertain risks. Furthermore, most surgeons have limited experience making these decisions, and existing decision-support tools are unhelpful.

The aim of this thesis was to improve the understanding of decision-making following severe lower limb trauma, and develop accurate prognostic models that can help identify those patients whose limb can be safely and effectively salvaged, and also identify those for whom attempts at limb salvage would be dangerous or fail.

The rationale for amputation decisions was analysed in a cohort of severe lower limb injuries (n = 579). Two prognostic models were designed to support difficult aspects of these decisions. Both models were developed using Bayesian networks that combine existing knowledge with individual patient data. The first provides early and accurate identification (AUROC = 0.927) of patients at risk of Trauma-Induced Coagulopathy, the principal indication for damage-control intervention. The model's performance in new patients, and ability to handle missing predictor information, was prospectively validated.

The second model accurately predicts the likely outcome, in terms of viability, of attempted limb salvage. This model outperformed the most widely used decision-support tool, the Mangled Extremity Severity Score (AUROC 0.932 versus 0.723; $P < 0.0001$). These Bayesian network tools accurately quantify critical risks that make rational judgement on the safety and effectiveness of interventions possible. This information enables individualised and evidence-based decisions, at a time when decision-making is most effective.

TABLE OF CONTENTS

CHAPTER FIVE

Validation of a predictive model for Trauma-Induced Coagulopathy

CHAPTER SIX

Meta-analysis of Prognostic Factors for Amputation following Lower-Extremity Vascular Trauma

LIST OF TABLES

LIST OF FIGURES

4.3 Structure of the Bayesian Network predictive model.

4.4 Overall accuracy of the trauma-induced coagulopathy predictive model.

4.5 Model calibration in the development cohort.

4.6 One-way sensitivity analyses of the impact individual predictor variables have on the models result.

CHAPTER FIVE

Validation of a predictive model for Trauma-Induced Coagulopathy

5.1 Kaplan-Meier estimates of the probability of survival for 491 injured patients with either normal coagulation or a coagulopathy.

5.2 Accuracy of the trauma-induced coagulopathy predictive model in the development and validation cohorts.

5.3 Area under the Receiver Operating Characteristic (ROC) curve with 95 per cent Confidence Intervals for trauma-induced coagulopathy predictions in 491 injured patients using individual predictors and the full predictive model.

5.4 Odds Ratios with 95 percent Confidence Intervals (CI) for trauma-induced coagulopathy in 491 injured patients, according to individual predictors and the full predictive model.

5.5 Performance of a Bayesian Network model at predicting trauma-induced coagulopathy in 491 injured patients when each of the models predictors, and all the blood gas variables, in turn, were omitted as inputs.

CHAPTER SIX

Meta-analysis of Prognostic Factors for Amputation following Lower-Extremity Vascular Trauma

6.1 PRISMA flow diagram of study selection process.

6.2 Forest plot of secondary amputation proportions for included studies.

6.3 Sensitivity analyses of methodological differences between included studies.

6.4 Funnel plot of effect size against sample size for 45 included studies.

6.5 Potential prognostic factors identified from the included studies and the evidence supporting an association with secondary amputation (2000 – 2012).

6.6 Absolute risk (pooled proportion) of secondary amputation according to identified demographic, injury, and treatment prognostic factors.

6.7 Relative risk (pooled Odds Ratio) of secondary amputation for identified demographic, injury, and treatment prognostic factors.

CHAPTER SEVEN

Development and Validation of a Prognostic Model for Limb Viability

7.1 Structure of the Bayesian Network prognostic model.

7.2 Overall accuracy of the limb viability prognostic model.

7.3 Model calibration in cohort of 508 severe lower limb injuries.

7.4 One-way sensitivity analyses of the impact individual predictor variables have on the models result.

7.5 Comparison of the Area Under the Receiver Operator Characteristic (AUROC) curve for predicting amputations performed because of a non-viable limb using a Bayesian Network prognostic model and the Mangled Extremity Severity Score (MESS).

CHAPTER EIGHT

Conclusions

8.1 Screenshots from the online evidence browser developed by Yet (2013) which is available at http://atcbn.traumamodels.com:8080 showing: A) an example of information on a variable (lactate) in the TIC model, and B) an example of information on a relation (hypoperfusion and lactate) in the TIC model.

8.2 Factors influencing the long-term functional outcome of trauma survivors with severe lower limb injuries.

LIST OF ABBREVIATIONS

ACIT	Activation of Coagulation & Inflammation in Trauma study
AIS	Abbreviated Injury Scale
AKA	Above-Knee Amputation
APTTr	Activated Partial Thromboplastin Time ratio
ATC	Acute Traumatic Coagulopathy
ATLS	Advanced Trauma Life Support
AUROC	Area Under the Receiver Operator Characteristic curve
BD	Base Deficit
BKA	Below-Knee Amputation
BN	Bayesian Network
BS	Brier Score
BSS	Brier Skill Score
CA5	Clot Amplitude at 5 minutes
CI	Confidence Interval
COAST	Coagulopathy of Severe Trauma score
CrI	Credible Interval
CT	Computer Tomography
DAG	Directed Acyclical Graph
DCO	Damage Control Orthopaedics
DCR	Damage Control Resuscitation
DCS	Damage Control Surgery
DOR	Diagnostic Odds Ratio
EBM	Evidence Based Medicine
EM	Expectation-Maximisation
FAST	Focused Assessment with Sonography for Trauma
FFP	Fresh Frozen Plasma
GCS	Glasgow Coma Scale
GHS	Ganga Hospital Score
GWOT-VII	Global War On Terror Vascular Injury Initiative
HDA	Hip-Disarticulation Amputation
HFS	Hanover Fracture Scale
HL	Hosmer and Lemeshow test
HR	Heart Rate
INR	International Normalised Ratio

IQR	Inter-Quartile Range
ISS	Injury Severity Score
ITU	Intensive Treatment Unit
JTTR	Joint Theatre Trauma Registry
LEAP	Lower Extremity Assessment Project
LEVT	Lower Extremity Vascular Trauma
LSI	Limb Salvage Index
MAI	Multiple level Arterial Injury
MESI	Mangled Extremity Syndrome Index
MESS	Mangled Extremity Severity Score
METALS	Military Extremity Trauma Amputation/Limb Salvage study
MOI	Mechanism Of Injury
NDM	Naturalistic Decision-Making
NISSSA	Nerve, Ischaemia, Soft tissue, Skeletal, Shock, Age score
NPT	Node Probability Table
OR	Odds Ratio
PRBC	Packed Red Blood Cells
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSI	Predictive Salvage Index
PT	Prothrombin Time
PTr	Prothrombin Time ratio
PTSD	Post Traumatic Stress Disorder
PTT	Partial Thromboplastin Time
ROC	Receiver Operating Characteristic curve
ROTEM	Rotational Thromboelastometry
RR	Relative Risk
SBP	Systolic Blood Pressure
SIP	Sickness Impact Profile
TBI	Traumatic Brain Injury
TIC	Trauma-Induced Coagulopathy
TKA	Through-Knee Amputation
TVS	Temporary Vascular Shunts
UK	United Kingdom
US	United States
USAISR	United States Army Institute of Surgical Research

KEY DEFINITIONS

I have used the generally accepted definitions of the following key terms that are used throughout this thesis:

Severe lower limb trauma:

A lower limb injury that poses a threat to the patient's life or the limb's viability, and requires either 1) emergency surgery for haemorrhage, ischaemia or compartment syndrome, 2) surgical reconstruction of the functional tissues (vessels, bone, soft tissue, nerve) or 3) amputation.

Traumatic amputation:

A traumatic amputation is the complete amputation of the extremity by the injuring force.

Primary amputation:

Primary amputation is the surgical amputation of an injured limb as the first operative procedure, either because it is decided that reconstruction is not technically possible or that reconstruction would be harmful.

Secondary amputation:

Secondary amputation is the surgical amputation of an injured limb as a secondary procedure following an initial attempt at limb salvage. Secondary amputation may be performed within hours of injury to many years after injury. Indications include non-viable tissue, infection, chronic pain, and functional limitations.

CHAPTER ONE

Introduction

1.1 The Significance of Severe Lower Limb Trauma

1.1.1 The Health Impact of Injuries

Injuries may be defined as any intentional or unintentional physical damage to the tissues of the body caused by an external force such as a road traffic collision, a fall, or violence (Smith et al., 2010). They are a global public health problem, with every member of society in every country of the world at risk. In 2010, injuries caused 11.2 percent of the world's burden of disease, including 5.1 million deaths (Lozano et al., 2012) and 47.2 million years lived with disability (Murray et al., 2012, Vos et al., 2012). To put this in context, injuries are responsible for more global disease burden than HIV/AIDS, TB and Malaria combined (8.6 percent); all neoplasms (7.8 percent); or ischaemic heart disease (5.2 percent), the leading individual cause of worldwide disease burden (Murray et al., 2012). Furthermore, injuries are one of the few causes of disease with an increasing global burden and this trend is predicted to continue (WHO, 2014).

Although all humans are at risk, injuries typically affect young, healthy, active members of society and males more than females. Ninety percent of the global injury burden occurs in low- and middle-income countries (WHO, 2014), however in high-income countries, injury remains the leading cause of death in the first four decades of life (CDC, 2010).

Substantially more injuries result in long-term disability than in death (Chandran et al., 2010). Approximately 80 percent of survivors of major injuries, defined as an Injury Severity Score > 15, (Gabbe et al., 2012, Ringburg et al., 2011, Evans et al., 2003) and a similar proportion of injured patients hospitalised for more than 24 hours (Polinder et al., 2007, Holbrook et al., 1999), continue to experience injury-related functional disabilities one year after injury. Few of these patients will experience any functional recovery beyond a year after injury (Holbrook et al., 1999, Gabbe et al., 2012, Polinder et al.,

2007). Up to a quarter of these patients experience severe disabilities that make them dependent on assistance for normal daily activities (Gabbe et al., 2012).

1.1.2 The Health Impact of Lower Limb Injuries

Musculoskeletal injuries are the most common reason for surgery following major trauma (Balogh et al., 2012) and an important contributor to global disability (Mock and Cherian, 2008). Although our understanding of injury-related causes of disability is poor compared to our understanding of injury-related causes of death, lower extremity injuries are consistently identified as major determinants of poor long-term functional outcome, and the resulting disability and dependence (Gabbe et al., 2012, Pape et al., 2010, Polinder et al., 2007, Holbrook et al., 1999, Holtslag et al., 2007, Ringburg et al., 2011). In low-income counties, such as Ghana, lower extremity injuries are the predominant cause of long-term disability (Mock et al., 2003). In developed countries, traumatic brain injury (Rosenfeld et al., 2012) and lower extremity injury (Pape et al., 2010, Brohi et al., 2011) are responsible for the majority of long-term injury-related disability.

A landmark group of studies, the Lower Extremity Assessment Project (LEAP), investigated outcomes of patients with major lower-extremity injuries (MacKenzie and Bosse, 2006). This large, multicentre, prospective observational study recruited adult patients at eight level-1 trauma centres in the United States and followed them up for seven years (MacKenzie et al., 2005). The results provide the best available evidence on which to base our understanding of the health impact of major lower limb trauma. Overall, it found that the disability resulting from these injuries is both profound and prolonged (Bosse et al., 2002, MacKenzie et al., 2005).

Physical Health

A 2002 LEAP publication in the New England Journal of Medicine (Bosse et al., 2002) reported the functional outcomes of patients two years after severe lower extremity

injuries. The primary outcome measure was the Sickness Impact Profile (SIP), a self-reported measure of health status (Bergner et al., 1981). The SIP measures an injury's impact on overall health and its impact in two major domains, physical and mental health. They found that patients with lower extremity injuries had substantially worse physical function than normal populations, with over 40 percent having severe physical disability. Although early functional improvements were observed, these had plateaued by two years, and beyond this significantly worsened with time (MacKenzie et al., 2005). By seven years after injury only one third of lower limb trauma patients had normal physical function with over half experiencing severe physical disability (MacKenzie et al., 2005). Population ageing and the development of secondary conditions, such as arthritis and chronic pain, may in part explain this physical deterioration.

Although the LEAP study describes the outcomes achieved at leading US level-1 trauma centres, similar high levels of profound physical disability following lower limb trauma have been reported in other high-income countries (Pape et al., 2010, Mkandawire et al., 2002), low-income countries (Mock et al., 2003) and the military (Doukas et al., 2013).

Mental Health

It is now recognised that survivors of major injuries are at increased risk of developing mental health disorders (Shih et al., 2010, Holbrook et al., 2005). Post-Traumatic Stress Disorder (PTSD), major depression, anxiety, and substance abuse are the most common and frequently co-exist (Shih et al., 2010, Hoge et al., 2004, Brown et al., 2000). Development of these disorders diminishes the patients' ability to cope with their physical disabilities and is an important determinant of poor long-term health outcomes (Wegener et al., 2011).

The LEAP study described the poor psychosocial outcomes of civilians with severe lower limb injuries. Seven years after injury, half of limb trauma patients had psychosocial outcomes worse than normal, with more than one third having severe psychosocial

disabilities. Furthermore, a significant deterioration in psychosocial functioning with time was observed (MacKenzie et al., 2005). In a more detailed assessment of psychological distress, the LEAP investigators revealed that almost half of the patients screened positive for a psychological disorder within two years of injury and reaffirmed that the disability did not improve with time (McCarthy et al., 2003). Although the LEAP studies did not screen for PTSD, one in five patients in their cohort developed severe phobic anxiety and a similar proportion of patients developed severe depression (McCarthy et al., 2003).

A meta-analysis of the psychological responses to civilian trauma showed a similar pattern of disorders to those developed in soldiers following military traumatic stress (Brown et al., 2000). This suggests a common psychopathology to major trauma, independent of mechanism or setting. The Military Extremity Trauma Amputation/Limb Salvage (METALS) study examined psychological outcomes following severe lower extremity injury in the recent wars in Afghanistan and Iraq (Doukas et al., 2013). They report high levels of psychological distress, mirroring the LEAP study results. At a mean follow-up time of three years post-injury, nearly one in five soldiers (18 percent) screened positive for PTSD and 13 percent had developed severe depression.

Chronic Pain

Acute pain normally accompanies tissue injury and will usually ease with healing. The development of chronic pain following injury is pathological. Chronic pain is highly prevalent after major trauma and is a leading cause of disability, lost productivity, and human suffering (Rivara et al., 2008). Furthermore, the development of chronic pain and/or mental health disorders can markedly impede functional recovery following injury (Wegener et al., 2011).

A number of observational studies have reported the prevalence of chronic pain in severe lower limb trauma populations (Table 1.1). The largest prospective study was performed

by the LEAP group (Castillo et al., 2006). They demonstrated significantly higher levels of chronic pain than in the general population. Seven years after injury only 23 percent of patients were pain free, while in 28 percent pain was severe enough to interfere with daily activities. These levels of chronic pain are comparable to other notable debilitating pain conditions such as backache and migraine headache (Castillo et al., 2006).

Table 1.1: Observational studies reporting the prevalence of chronic pain in populations with severe lower limb injuries.

Reference	Study type	Sample Size	Follow-up (months)	Setting	Chronic pain		Outcome Measure[a]
					Overall	Severe	
Soni et al. (2012)	Retro	18	60	Civilian	72 %	11 %	EQ-5D
Mkandawire et al. (2002)	Retro	25	60	Civilian	80 %	12 %	Pain scale
Gopal et al. (2004)	Retro	33	46	Civilian	45 %	3 %	EQ-5D
Georgiadis et al. (1993)	Retro	34	44	Civilian	74 %	9 %	Pain scale
Hertel et al. (1996)	Retro	44	83	Civilian	68 %	7 %	VAS
Hoogendoorn (2001)	Retro	56	n/a	Civilian	55 %	13 %	Pain scale
Giannoudis et al. (2009b)	Retro	67	37.4	Civilian	51 %	9 %	EQ-5D
Mock et al. (2000)	Prosp	302	12	Civilian	66 %	17 %	VAS
Doukas et al. (2013)	Retro	324	37.5	Military	n/a	20 %	CPG
Castillo et al. (2006)	Prosp	397	84	Civilian	77 %	28 %	CPG

Retro, Retrospective; Prosp, Prospective; n/a, not available.

[a] EQ-5D (Rabin and Charro, 2001); VAS, Visual Analogue Scale (Scott and Huskisson, 1976); CPG, Chronic Pain Grade Scale (Von Korff et al., 1992); Pain scale, Authors' own pain scale.

1.1.3 Factors that Influence the Health Impact of Severe Lower Limb Injuries

There is a wide variation in functional outcome after major lower-extremity trauma that cannot be explained by the injury or injury treatment alone (MacKenzie and Bosse, 2006, Mock and Cherian, 2008). Using regression analysis, a number of additional factors that influence outcome have been identified, and together, may explain the majority of outcome variance (Bosse et al., 2002, MacKenzie et al., 2004). Broadly these can be divided into pre-injury, injury and post-injury factors (Figure 1.1).

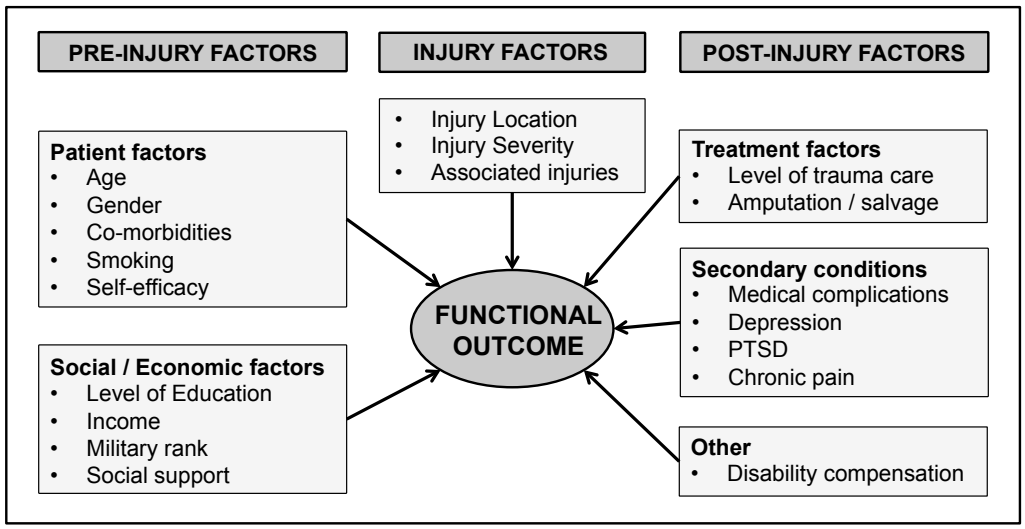


Figure 1.1: Factors influencing the long-term functional outcome of trauma survivors with severe lower limb injuries.

Pre-injury factors

Older age, female gender and presence of co-morbidities are well-described risk factors for poor functional outcomes after major trauma (Gabbe et al., 2012, Holbrook et al., 1999, Holbrook and Hoyt, 2004, Holtslag et al., 2007, Polinder et al., 2007) and severe lower limb trauma (Doukas et al., 2013, MacKenzie et al., 2005, Mock and Cherian, 2008). Smoking and low self-efficacy have also been identified as important predictors of poor outcome in patients with severe lower limb injuries (MacKenzie et al., 2005), and these factors may be more amenable to modification. The LEAP study highlighted the impact that social and economic factors have on determining eventual functional outcome. In civilian lower-extremity trauma populations, poverty, low level of education and poor social support are independently associated with worse outcomes (MacKenzie et al., 2005, Mock and Cherian, 2008), while military rank and poor social support are independently associated with worse outcomes in military lower-extremity trauma populations (Doukas et al., 2013). Possible reasons for these associations include poverty and level of education being markers of access to health and rehabilitation care (MacKenzie and Bosse, 2006), and lower military rank being a marker of more intense combat experience

with a higher risk of developing complications such as depression and PTSD (Doukas et al., 2013).

Injury factors

The location and degree of tissue destruction following severe lower limb trauma, together with the treatment of these injuries, are the primary determinants of functional outcome. However, pre- and post-injury factors also have an important influence on eventual outcome.

Post-injury factors

There is growing evidence that the level of trauma care is an important predictor of long-term functional outcomes after injury. Treatment at a specialised trauma centre is associated with improved outcomes in both major trauma (Gabbe et al., 2012) and severe lower limb trauma populations (Mackenzie et al., 2008).

Secondary conditions such as treatment complications (Harris et al., 2009), chronic pain (Castillo et al., 2006), and psychological disorders (McCarthy et al., 2003), also influence outcome, and the development of these conditions is common following severe lower limb injuries. Although these secondary conditions have previously been recognised as independent predictors of poor functional outcome after trauma (Holbrook et al., 1999, Mock et al., 2000), only in recent years has the major impact on functional outcomes been appreciated (Wegener et al., 2011).

The relationship between gender, chronic pain and psychological morbidity may in part explain the gender difference in functional outcomes after severe lower limb injuries. Females are at particular risk of developing secondary psychological disorders, with significantly higher rates of post-injury depression and PTSD than males (Holbrook et al., 2002, Holbrook et al., 2001). Chronic pain is also more common in females and in patients that develop secondary psychological disorders (Castillo et al., 2006).

An additional risk factor for developing chronic pain after lower-extremity injury is the intensity of acute pain during recovery; while opiate analgesia, high self-efficacy, and a higher level of education seem to be protective (Castillo et al., 2006).

Finally, involvement in compensation litigation is associated with worse functional outcomes in major trauma (Harris et al., 2008) and major lower-extremity trauma populations (MacKenzie et al., 2005, Mock et al., 2000).

1.1.4 Military Lower Limb Injuries

Advances in body armour and military medicine have resulted in improved survival and a change in wounding patterns of injured soldiers (Owens et al., 2008). As a result, severe extremity trauma has become the predominant injury in modern warfare (Owens et al., 2007). Injured soldiers differ in important ways from injured civilian populations. Most importantly, the mechanism of injury in modern warfare is predominantly high-energy blasts. Other important differences include: 1) soldiers are on average younger, 2) in better pre-injury physical condition, 3) have unmatched access to excellent trauma care, rehabilitation and prosthetic services and 4) have robust support networks. For these reasons, outcomes following severe lower extremity trauma may be different in soldiers than in civilians (MacKenzie and Bosse, 2006).

1.2 Contemporary Management of Severe Lower Limb Trauma

1.2.1 Advances in Trauma Care

Recent decades have seen major advances in the management of injured patients. Many of these advances impact the outcome of patients with severe lower limb trauma. This progress spans resuscitation, reperfusion, reconstruction, and rehabilitation, and in many respects, has been driven by military innovation. Limb salvage is now potentially possible in patients that would historically have died or required an amputation. In parallel, radical advances in prosthetic technology and rehabilitative medicine have improved the outcome of amputees.

Resuscitation

The concepts of damage control, which focus on rapidly restoring normal physiology in exsanguinating patients, have redefined trauma resuscitation (Shapiro et al., 2000). Early haemorrhage control combined with the management of coagulopathy have been recognised as central to outcome, and Damage Control Resuscitation (DCR) aims to directly address these endeavours (Jansen et al., 2009, Holcomb et al., 2007a, Duchesne et al., 2010a). DCR involves early haemostatic resuscitation with blood products, rather than the traditional crystalloid fluids, and the tolerance of moderate hypotension until haemorrhage control is imminent. Damage Control Surgery (DCS) (Shapiro et al., 2000, Rotondo et al., 1993) involves abbreviated techniques to stop haemorrhage, minimise contamination, and restore limb perfusion (Rasmussen et al., 2006b); while Damage Control Orthopaedics (DCO) (Giannoudis et al., 2009a, Pape, 2008) involves abbreviated techniques to provide skeletal stabilization and optimize soft tissue perfusion. Both DCS and DCO are performed simultaneously with DCR and aim to support effective resuscitation while limiting further harm.

Major advances in pre-hospital care facilitate these damage control principles and include earlier access to effective resuscitation and haemorrhage control strategies, and expeditious evacuation to appropriate medical facilities. Notable with regard to severe limb trauma is the newly defined role of tourniquets in modern trauma care, for temporary extremity haemorrhage control (Kragh et al., 2009).

Reconstructive surgery

Surgical advances in 1) vascular repair and reconstruction, 2) fracture fixation and bone reconstruction, 3) microvascular free tissue transfer and, to a lesser degree, 4) nerve reconstruction, have allowed limb salvage to replace amputation as the primary treatment for severe lower limb trauma (Wagels et al., 2013). Together with the time-tested principles of debridement and antisepsis, these modern advances in surgery form the pillars of limb reconstruction. Recent advances in wound management, such as negative pressure wound therapy, may also have a considerable impact on the management of severe lower limb injuries (Couch and Stojadinovic, 2011, Nanchahal J, 2009).

Rehabilitation and prosthesis technology

Remarkable advances in prosthetic components and materials, including breakthrough innovations in shock absorption, prosthetic joints and osseo-integration, have created more comfortable, efficient and life-like artificial limbs. These advances have afforded amputees remarkable functional levels and improved the quality of their lives (Laferrier and Gailey, 2010, Marks and Michael, 2001).

1.2.2 Principles of Lower Limb Trauma Management

1.2.2.1 Pre-operative interventions

Control haemorrhage

Exsanguination from an extremity injury is a leading cause of preventable military death (Holcomb et al., 2007b, Mabry et al., 2000, Kelly et al., 2008). Although less common, civilian deaths from extremity exsanguination do occur (Dorlac et al., 2005). Consequently, control of catastrophic haemorrhage is the first clinical priority when treating a patient with severe lower limb injuries, which can usually be achieved with direct pressure and limb elevation. If haemorrhage continues a tourniquet is indicated. In extreme situations, such as those involving mass casualties or where rescuer safety is at risk, a tourniquet may be the primary means of extremity haemorrhage control. When indicated, correct tourniquet application improves survival with minimal associated morbidity (Kragh et al., 2009) (Kragh et al., 2008). Furthermore, early application improves effectiveness, particularly if applied before clinical signs of shock develop (Kragh et al., 2009).

Incorrect application and prolonged use may result in iatrogenic morbidity and possible mortality. Skeletal muscle is the most vulnerable limb tissue to ischaemia. Animal and human studies suggest muscle may tolerate warm ischaemia for up to three hours, following this progressive and severe myonecrosis occurs (Blaisdell, 2002, Glass et al., 2009). The amount of ischaemic muscle damage not only affects limb viability, it is also a critical aspect of reperfusion injury (Percival and Rasmussen, 2012). To minimise risk, the continued need for an emergency tourniquet should be reviewed at the earliest possible opportunity, preferably within two hours of application.

Prevent pain

Opiate or Ketamine analgesia should be administered as soon after injury as possible. Not only do these agents control acute pain, they may also reduce the risk of chronic pain (Huse et al., 2001, Nikolajsen et al., 1996). Painful symptoms before amputation are associated with an increased risk of phantom limb pain (Flor, 2002, Nikolajsen and Jensen, 2001) and pre-emptive analgesia may disrupt the development of pain memories that are central to chronic pain pathogenesis (Katz and Melzack, 1990). Several studies suggest that pre-emptive analgesia with epidural anaesthesia may also reduce the incidence of phantom limb pain (Bach et al., 1988, Jahangiri et al., 1994). However, a randomised, double-blinded study showed no benefit and highlighted the risks of epidural anaesthesia (Flor, 2002). An important limitation of this study is that the sample population required amputation for chronic pathology, so epidural analgesia was not truly pre-emptive, as central nervous system changes may have already been established. The role of pre-emptive epidural anaesthesia in the acute limb trauma population has therefore not yet been clearly defined.

Minimise contamination

Infections are a common complication and an important source of morbidity following severe lower limb injuries. The infection risk is directly related to injury severity, and wound infections occur in approximately one quarter of civilian (Pollak et al., 2010) and military (Brown et al., 2010) mangled extremities.

The most important step in minimising infection risk is operative debridement. Pre-operative management should simply aim to remove gross contamination, seal the wound, and administer antibiotic prophylaxis (Nanchahal J, 2009, Murray et al., 2008). Pre-operative wound exploration, debridement and irrigation may drive infection deeper into tissues and should be avoided (Nanchahal J, 2009). Repeated wound inspections and dressing changes also promote infection. To minimise this, wounds should be photographed, covered with a sterile, saline soaked dressing and sealed with an adhesive

film to minimise evaporation (Nanchahal J, 2009). Dressings and wounds should not be soaked in povidone-iodine antiseptics. The antimicrobial activity after exposure to blood is disputable, and the resulting tissue staining makes the assessment of tissue viability at debridement difficult. Furthermore, absorption of iodine in large open wounds can result in local and systemic toxicity (Nanchahal J, 2009, Misra and Nanchahal, 2003).

Early administration of prophylactic antibiotics is a standard of care and of proven value in reducing the risk of infection (Gosselin et al., 2004, Hoff et al., 2011). In military and civilian settings, antibiotics should be administered as soon as possible, preferably within 3 hours of injury (Patzakis and Wilkins, 1989, Jackson, 1984, Hauser et al., 2006, Nanchahal J, 2009). Guidelines on the choice of antibiotic and duration of prophylaxis are summarized in Table 1.2. Routine wound cultures are not recommended and should only be obtained to guide treatment when infection is clinically suspected (Murray et al., 2008). Tetanus status should be checked and prophylaxis administered if required.

1.2.2.2 Emergency operative interventions

The best outcomes are achieved when patients with severe limb injuries are managed in specialist trauma centres by experienced multidisciplinary teams that include combined orthopaedic and plastic surgical care (Mackenzie et al., 2008, Nayagam et al., 2011, Nanchahal J, 2009). Direct triage, or immediate referral, of patients with these injuries to such units is justified. Emergency limb surgery is indicated when uncontrolled haemorrhage, compromised perfusion, compartment syndrome, or gross contamination are present. All other limb surgery should only take place after resuscitation and normalisation of physiology (Nanchahal J, 2009).

Wound debridement

Meticulous excision of devitalised tissue followed by wound irrigation is the most important intervention in reducing infection risk. The timing is controversial, urgent

surgery within six hours of injury is a widely accepted standard, but not supported by evidence (Crowley et al., 2007a). Delays of up to 24 hours do not increase infection risk or worsen outcome (Webb et al., 2007, Pollak et al., 2010, Naique et al., 2006, Crowley et al., 2007a). The best outcomes are achieved when an experienced ortho-plastic team performs scheduled surgery within 24 hours of injury (Nanchahal J, 2009).

All viable tissue must be preserved, flaps should not be fashioned and no part of the wound should be closed at initial operation (Clasper, 2007, Tintle et al., 2010b). Removal of viable tissue at his stage may compromise limb reconstruction and eventual outcome. Wounds may however, be extended along faciotomy lines to improve exposure and facilitate complete excision of devitalised tissue. As wounds are evolving, a second procedure should be undertaken in 24 to 48 hours; further staged procedures may be required. Accurate technique is important to avoid excessive procedures, which may worsen outcome (Park et al., 2002).

Guillotine amputations must be avoided (Mannion and Chaloner, 2005, Coupland, 1989, Clasper, 2007, Tintle et al., 2010b, Fergason et al., 2010). The only exception is as a pre-hospital emergency procedure to relieve entrapment in an immediately life-threatening situation (Porter, 2010).

Wound irrigation

Wound irrigation with sterile saline is performed after adequate debridement. Antibiotic and antiseptic additives should be avoided (Crowley et al., 2007b, Anglen, 2005). A low-pressure (< 15psi) irrigation method using the traditional fluid volume of at least nine litres is recommended (Crowley et al., 2007b, Nanchahal J, 2009). High-pressure pulsed lavage, especially above 50 psi, should be avoided as it may result in tissue damage and may drive bacteria deeper into wounds (Crowley et al., 2007b).

Table 1.2: Guidelines for antibiotic prophylaxis in patients with severe open fractures of the lower limb.

Reference	Association	Antibiotic	Duration	Additional comments
Nanchahal J (2009)	BOA and BAPRAS	Co-amoxiclav 1.2 grams 8-hourly IV or Cefuroxime 1.5 grams 8-hourly IV. Single dose of Gentamicin (1.5mg/kg) on induction of anaesthesia (debridement and reconstruction). Single dose of Vancomycin 1gram or Teicoplanin 800mg on induction of anaesthesia (reconstruction).	Until soft tissue closure or a maximum of 72 hours, whichever is sooner	Mild penicillin allergy use cephalosporin. Severe penicillin allergy use Clindamycin 600mg 6-hourly IV.
Hoff et al. (2011)	EAST	Systemic antibiotic with gram positive and gram negative cover	72 hours or not more than 24 hours after soft tissue coverage achieved	Add Penicillin in suspected faecal or clostridial contamination.
Hauser et al. (2006)	SIS	1st generation Cephalosporin	24 – 48 hours	Insufficient evidence to support additional gram negative or clostridial cover, prolonged courses or repeat short courses.
Dufour D (1998)	ICRC	Penicillin G 5MIU 6-hourly IV for 48 hours followed by Penicillin V 500mg 6-hourly orally.	5 days or until delayed primary closure	Add Metronidazole in land mine injuries and delays to treatment of > 72 hours.

BOA: British Orthopaedic Association
BAPRAS: British Association of Plastic, Reconstructive and Aesthetic Surgeons
EAST: Eastern Association for the Surgery of Trauma
SIS: Surgical Infection Society
ICRC: International committee of the Red Cross

Temporary wound dressing

The ideal temporary wound dressing would prevent bacterial ingress, avoid tissue damage and desiccation, and not require regular changing. Negative pressure wound therapy

meets many of these criteria and has dramatically changed the way complex traumatic wounds are managed (Orgill and Bayer, 2011, Couch and Stojadinovic, 2011, Nanchahal J, 2009). Randomised control trials support the improved wound healing and reduced infection risk of this therapy (Moues et al., 2004, Stannard et al., 2009). The use of antibiotic bead pouches in complex wounds may also reduce infection rates compared to systemic antibiotics alone (Nanchahal J, 2009).

1.2.2.3 Definitive operative intervention

Limb reconstruction

Over the past few decades there have been tremendous advances in the ability to reconstruct limb trauma. It has now become technically possible to reconstruct severe lower limb injuries that would previously have mandated amputation. This has not made decision-making simpler, on the contrary, decisions now not only need to consider whether limb salvage is possible, but also the more complex question of whether a salvaged limb would produce a better outcome than would be achieved by an amputation with prosthesis. Nonetheless, these advances in vascular, soft tissue, and orthopaedic reconstruction, have transformed the outcomes of patients who suffer severe lower limb trauma.

Vascular reconstruction

In 1912, a French surgeon, Alexis Carrel, was awarded the Nobel Prize for his pioneering work developing vascular suturing techniques. These techniques form the basis of modern day vascular reconstruction. However, despite this knowledge, reconstruction of vascular injuries was rarely performed for many decades following Carrel's descriptions. Ligation was still the standard surgical treatment for arterial trauma in World War II (1939 – 1945) (DeBakey and Simeone, 1946). The results were poor, with amputation rates of 81 percent following ligation of the common femoral artery, 55 percent following

ligation of the superficial femoral artery, and 73 percent following ligation of the popliteal artery (DeBakey and Simeone, 1946). By the end of World War II (1945), as these dismal outcomes became clear, there was a shift towards arterial repair, with improved limb salvage rates (Barr et al., 2015). Advances in the repair of vascular injuries continued during the Korean War (1950 – 1953) (Hughes, 1958). And by the Vietnam War (1955 – 1975), vascular reconstruction had become the standard of care for arterial trauma (Rich et al., 1970). The results of limb salvage had substantially improved, with amputation rates reduced to thirteen percent following reconstruction of extremity vascular trauma (Rich et al., 1970).

Many of the principles fundamental to reconstruction of vascular injuries were developed during these 20th century wars. Vascular reconstruction should be performed under general anaesthesia with sufficient blood products available for transfusion if required. The injury should be adequately exposed with proximal and distal control of involved vessels. High-energy injuries may cause extensive intimal damage; therefore the injured vessel should be carefully debrided until normal intima is seen. Next, proximal and distal arterial thrombus is removed using an embolectomy catheter followed by irrigation with heparin/saline solution. Definitive vascular reconstruction is then performed using an appropriate technique. Simple lacerations may be repaired with a lateral suture or patch angioplasty, while transected or debrided vessel edges, which can be approximated without any tension, may be reconstructed with an end-to-end anastomosis. If tension-free approximation is not possible, an interposition graft is indicated. Autologous vein is the preferred interposition conduit for definitive reconstruction (Mitchell Iii and Thal, 1990). However prosthetic grafts may have advantages in certain situations, for example as a temporary conduit during Damage Control procedures or when suitable autologous vein is not available (Feliciano et al., 1985, Vertrees et al., 2009). Concomitant deep venous injuries proximal to the trifurcation should also be reconstructed where possible (Kuralay et al., 2002).

The outcome of vascular reconstruction, and limb salvage, is critically dependant on the duration of ischaemia (Glass et al., 2009). Delayed reperfusion risks irreversible damage to the functional limb tissues, increased amputation rates, and potentially life-threatening reperfusion complications (Glass et al., 2009, Percival and Rasmussen, 2012). Therefore, extremity vascular injuries need to be recognised quickly and managed as a surgical emergency. The aim is to restore limb perfusion as quickly as possible, ideally within three to four hours of injury (Glass et al., 2009, Nanchahal J, 2009).

Careful clinical examination remains the cornerstone of vascular injury diagnosis, with adjunct Doppler examination if necessary. Patients with hard signs of a vascular injury should undergo immediate surgical exploration (NICE, 2016, Nanchahal J, 2009). Revascularisation should not be delayed for formal angiography as this may worsen outcome (Glass et al., 2009, NICE, 2016). If imaging is required an on-table angiography is preferable. A CT angiogram may be considered in patients with multiple injuries that require a CT scan as part of their initial assessment, or in patients where the site of vascular injury is unclear (NICE, 2016).

Temporary Vascular Shunts (TVS) are an important adjunct to vascular reconstruction that can reduce the duration of ischaemia significantly (Glass et al., 2009). By enabling early limb perfusion, TVS are particularly valuable in situations where the patient needs to be transferred to a higher level of care, other life-threatening injuries need to be managed (Damage Control), or time is required for safe skeletal fixation or careful wound assessment, prior to definitive vascular repair. TVS have proved safe and effective adjuncts to the management of both civilian (Subramanian et al., 2008) and military (Rasmussen et al., 2006b) extremity vascular trauma. In severe lower limb injuries with co-existing fractures, the most effective sequence of interventions, to reduce the duration of ischaemia and improve functional limb salvage, appears to be: direct exploration, TVS, skeletal fixation, followed by definitive vascular and soft tissue repair (Glass et al., 2009).

Skeletal reconstruction

Skeletal stability is required to facilitate wound healing and protect vascular and soft tissue reconstructions (Nanchahal J, 2009). Intramedullary nailing is the procedure of choice for closed fractures of the femoral and tibial shaft (Giannoudis et al., 2006). Open fractures may be definitively treated with internal or external fixation (Bhandari et al., 2001, Giannoudis et al., 2006). The choice is determined by the anatomy of the fracture, degree of tissue loss, degree of contamination, and timing of soft tissue cover (Nanchahal J, 2009). For severe open fractures, a combined orthoplastic approach, that allows immediate internal fixation and soft tissue coverage with muscle flaps, is safe and provides good results (Gopal et al., 2000). In physiologically compromised patients, who may not be able to withstand definitive fracture fixation, provisional skeletal stabilisation may be accomplished with a spanning external fixator. This strategy is termed Damage Control Orthopaedics (DCO) (Scalea et al., 2000, Giannoudis et al., 2009a). If DCO is used, definitive stabilisation should be performed as soon as possible after the patient has recovered, preferably within 72 hours of injury (Nanchahal J, 2009).

Soft tissue reconstruction

All exposed fractures, metalware, tendons, and neurovascular structures should be covered with vascularised soft tissue. Together with adequate wound debridement, early definitive soft tissue cover is essential to reduce infection complications and allow healing (Godina, 1986). For optimal results, definitive soft tissue cover should be achieved within 72 hours of injury. However, in situations where exposed vascular structures and metalware are present, definitive soft tissue cover should be achieved immediately (Liu et al., 2012).

Small defects with a limited zone of injury may be covered with local fasciocutaneous or muscle flaps, while larger defects frequently require transfer of healthy donor tissue to achieve adequate cover (Nanchahal J, 2009). Microsurgery techniques that allow free tissue transfer have revolutionised lower limb reconstruction (Godina, 1986). These free

flaps, which may be fasciocutaneous, muscle, bone, or a combination (Chimeric), allow reconstruction of almost any defect. The choice of flap is determined by the injury characteristics. For example, defects around joints are best covered with fasciocutaneous flaps, while muscle flaps may improve healing of open shaft fractures (Nanchahal J, 2009). Free flap reconstruction should, however, be performed by an experienced team, in a specialist centre, following adequate patient preparation (Nanchahal J, 2009).

Nerve reconstruction

Peripheral nerve injuries that produce loss of function may be classified according to the degree of nerve damage into neurapraxia (intact nerve), axonotmesis (disruption of axon with preservation of supporting structure), and neurotmesis (complete disruption of nerve) (Seddon, 1943, Sunderland, 1951). Full functional recovery is expected following neurapraxia and spontaneous recovery is possible following axonotmesis. Nerve injuries that do not recover spontaneously (neurotmesis and some axonotmesis) remain a challenging and difficult surgical reconstruction problem. Nerve reconstruction techniques include external neurolysis, end-to-end repair, nerve graft, and nerve transfer (Spinner and Kline, 2000). However, functional outcomes following attempts to repair injured lower limb nerves are generally poor (Lundborg, 2000), and a complete transection of a major lower limb nerve remains an important consideration for amputation (Lange et al., 1985). Although our understanding of nerve regeneration and brain plasticity continues to improve, new breakthroughs that allow us to translate this knowledge into clinical applications that improve outcomes are needed (Lundborg, 2000).

Residual limb reconstruction

Residual limb reconstruction should be planned once the wound appears clean and free from non-viable tissue. For optimal outcome, reconstruction should aim to preserve the maximum limb length possible with adequate soft tissue cover. Amputation in the zone of injury may increase the risk of wound complications in the short-term, but this is offset

by an improvement in overall outcome. Every effort should be made to preserve viable bone and functional joints. Amputation at the level of a fracture should be avoided if distal viable bone and soft tissue is present. These proximal fractures should be managed with standard fracture reduction and fixation techniques (Gordon et al., 2010, Clasper, 2007).

At the planned level of amputation, careful attention to the distal bone ends will avoid unnecessary morbidity. The tibia or femur should be beveled anteriorly and the edges carefully smoothed. The fibula should be shortened by three to four centimeters more than the tibia and sculpted smooth (Smith and Fergason, 1999, Bourke et al., 2010). The role of a bone bridge between the distal tibia and fibula in traumatic amputees is controversial (Pinzur et al., 2007). This technique may improve tibio-fibular instability, enhance weight bearing and improve functional outcome (Pinzur et al., 2006), although more reliable evidence supporting these benefits is required (Pinzur et al., 2008).

Soft tissue reconstruction must provide sufficiently durable and comfortable padding over the residual bone to allow optimal prosthesis use. This is achieved with a firmly secured myocutaneous flap. The most distal level of viable soft tissue should dictate the level of amputation (Clasper, 2007). At this level standard amputation flaps are frequently compromised by the injury. To preserve length, the available soft tissue ("flaps of opportunity") should be used to reconstruct the soft tissue envelope (Tintle et al., 2010b). This atypical flap coverage does not increase wound complications (MacKenzie et al., 2004). Other reconstructive surgical techniques to preserve limb length include skin grafts (Anderson et al., 2002), tissue expansion (Wieslander et al., 1996), and tissue transfer with pedicled (Ghali et al., 2005) or free flaps (Kasabian et al., 1991, Erdmann et al., 2002). Length preservation must not however, be at the expense of adequate soft tissue coverage as this may result in a painful, non-healing residual limb that cannot be used.

A second function of the soft tissue reconstruction is to restore muscular control to the residual limb. Loss of normal muscle attachments results in muscular imbalance, contractures and reduced function (Gottschalk, 1999). This is most marked in trans-femoral amputees where loss of adductor magnus attachment results in a flexion-abduction deformity that contributes to an inefficient gait. Myodesis of detached muscle groups to the residual bone will preserve normal anatomic and mechanical alignment and optimise function (Gottschalk, 1999). Myodesis is achieved by suturing residual muscle, under physiological tension, directly to the periosteum or bone through drill holes (Tintle et al., 2010b). Myodesis is recommended for traumatic amputations as it improves outcome (Gottschalk, 1999, Pinzur et al., 2007, Persson, 2001).

The management of nerves in a lower limb amputation

Neuroma formation cannot be prevented following nerve transection. However, only 10 to 25 percent of neuromas become symptomatic, usually because they are exposed to mechanical stimulation. Accurate surgical management of the nerve ending reduces the incidence of symptomatic neuromas. All named nerves should be identified. Using traction, each should be cut as proximal as possible, allowing the end to retract into the soft tissues, away from the stump. For trans-tibial amputations the sural nerve requires particular attention to prevent inclusion in the scar. A novel microsurgical technique, the sciatic nerve sling, may also reduce chronic post-amputation pain (Prantl et al., 2006).

1.3 Decision-Making following Severe Lower Limb Trauma

1.3.1 Defining the Problem

Deciding on the most beneficial method of treatment for a patient with a severely injured lower limb is complex and often difficult (Scalea et al., 2012, de Mestral et al., 2013). All patients want their injuries to be reconstructed, and their limbs to be salvaged. Major advances in reconstructive surgery have made this technically possible for the majority of injuries. However, there are a number of situations where this approach can cause significant harm. Patients with life-threatening injuries may not have the physiological reserve to tolerate complex and lengthy reconstructive procedures (Shapiro et al., 2000). Attempting definitive surgery in such patients may interfere with resuscitative interventions and result in deaths that could otherwise be prevented. Harm may also be caused in patients with injuries that are beyond repair. Prolonged and ultimately futile attempts at reconstruction may cause substantial physical and psychological morbidity that could be avoided with earlier amputation (Bondurant et al., 1988, Hansen Jr, 1989). Furthermore, some technically salvaged limbs may be more disabling than limb amputation combined with modern prostheses and rehabilitation.

Recognising which situation applies to an individual patient is difficult because the risks, benefits, and outcomes of different treatment strategies are uncertain when these decisions need to be made. In particular, limb amputation is clearly an irreversible procedure that commits the patient to a definite functional and physical impairment, while the comparative risks of salvage may not be immediately evident. Furthermore, delaying decisions until risks are clear can worsen outcome, and errors in judgement may have considerable consequences including unnecessary amputation or death.

1.3.2 Goals of Contemporary Management

The fundamental goal of the surgical management of severe lower limb trauma is to provide the patient with the most functional limb, or residual limb, possible. Implicit to this goal is the patient surviving their injury. So clinical decision-making is not simply whether salvage is technically possible but a more complex decision process that takes into account the risk of death with each treatment option and whether salvage will produce a better long-term functional outcome than an amputation with prosthesis would achieve. Not only do these decisions need to avoid unnecessary death or limb amputation, but also minimise the profound disability associated with prolonged attempts at futile limb salvage.

1.3.3 Guidelines for the Management of Severe Lower Limb Trauma

To aid in the complex decision-making, a number of guidelines have been developed that are relevant to the management of severe lower limb trauma (Table 1.3).

The key principles common to these guidelines are:

Resuscitation

a) The initial evaluation of the patient with a severe lower limb injury remains the same as for any patient with serious injuries. A systematic approach that facilitates the rapid identification and simultaneous management of life-threatening injuries should be used.
b) The treatment of life-threatening injuries takes priority over limb-threatening injuries.
c) Active haemorrhage is the only immediate life threat resulting from severe lower limb injuries and must be rapidly controlled with direct pressure. Uncontrolled haemorrhage requires emergency surgery. In these situations, the temporary application of a tourniquet, until surgical control is achieved, may be life saving.

d) Limb ischaemia is the most important limb-threatening condition. Injuries that result in limb ischaemia must be recognised promptly and treated as an emergency.

Surgery

a) Limb salvage is critically dependent on ischaemic time. Early insertion of temporary vascular shunts may significantly reduce ischaemic time allowing timely resuscitation, wound evaluation, fracture stabilisation and definitive vascular repair.
b) Formal operative wound evaluation is essential to inform definitive limb management decision-making.
c) Initial limb surgery should include liberal use of compartment faciotomies.
d) Limb amputation may be a necessary procedure to achieve an optimal outcome and is not a failure of surgical management.
e) Definitive limb or residual limb reconstruction should only be considered in patients with normal physiology, which has recovered from any initial derangements.

Table 1.3: Management guidelines relevant to severe lower limb trauma.

Reference	Title	Association
NICE (2016)	Major Trauma: Complex Fractures (draft guideline)	NICE
Feliciano et al. (2013)	Western Trauma Association Critical Decisions in Trauma: Evaluation and management of peripheral vascular injury, Part II.	WTA
Fox et al. (2012)	Evaluation and management of penetrating lower extremity arterial trauma: An Eastern Association for the Surgery of Trauma practice management guideline.	EAST
Scalea et al. (2012)	Western Trauma Association Critical Decisions in Trauma: Management of the mangled extremity.	WTA
Feliciano et al. (2011)	Evaluation and Management of Peripheral Vascular Injury. Part 1. Western Trauma Association/Critical Decisions in Trauma	WTA
Feliciano (2010)	Management of peripheral arterial injury	n/a
Nanchahal J (2009)	Standards for the management of open fractures of the lower limb.	BOA and BAPRAS
Glass et al. (2009)	Improving lower limb salvage following fractures with vascular injury: a systematic review and new management algorithm.	n/a
Gillespie (2008)	Clinical practice guidelines for vascular injury	JTTS
ACS (2005)	Management of Complex Extremity Trauma	ACS
Feliciano (2002)	Management of the mangled extremity	ACS

EAST, Eastern Association for the Surgery of Trauma; WTA, Western Trauma Association; BOA, British Orthopaedic Association; BAPRAS, British Association of Plastic, Reconstructive and Aesthetic Surgeons; JTTS, Joint Theatre Trauma System; ACS, American College of Surgeons Committee on Trauma. n/a, not applicable

1.3.4 Key Decisions in Severe Lower Limb Trauma Management

The key management decisions emphasised in the lower-extremity trauma management guidelines are summarised in figure 1.2. For optimal decision-making, an understanding of the important elements of each decision is required. These include 1) the time frame available, 2) the ideal information required for optimal decision-making, 3) the actual

information available given the time frame, and 4) how an accurate decision will benefit a patient with severe lower limb injuries.

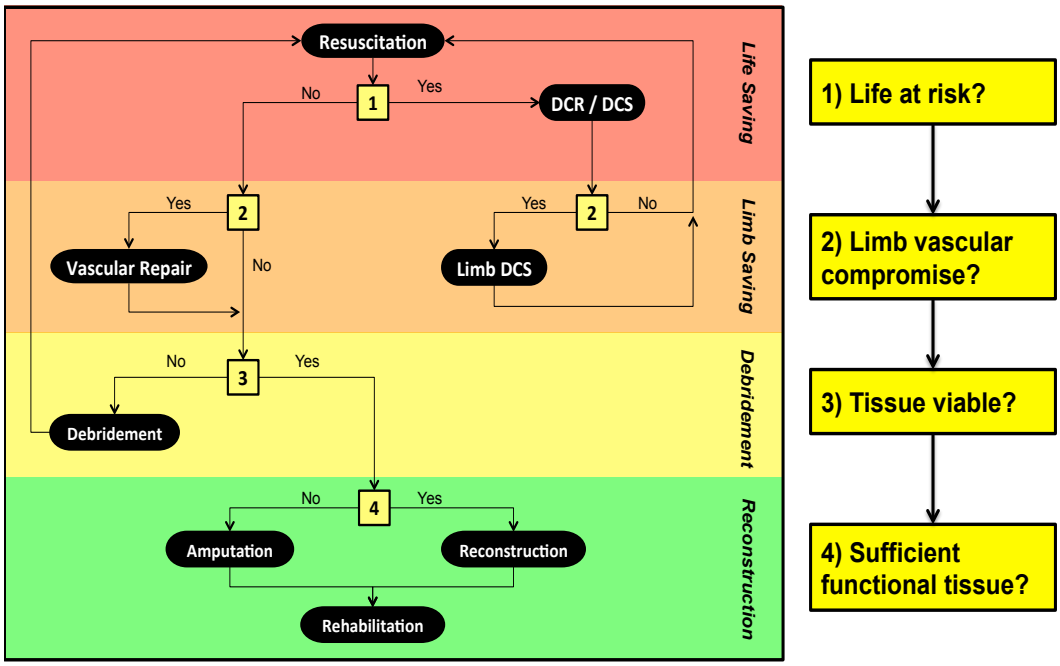


Figure 1.2: Contemporary management of severe lower limb trauma and corresponding decision-making. DCS: Damage Control Surgery.

Decision One: Is the patient's life at Risk?

The first decision involves deciding which patients will benefit from definitive care and which would benefit from a Damage Control approach to resuscitation and surgery. This decision needs to be made as soon as possible after injury, ideally within a few minutes of hospital arrival, or possibly even during the pre-hospital phase. Damage Control is of benefit to bleeding patients whose physiology is compromised by tissue hypoperfusion and coagulopathy (Roberts et al., 2015). This group of patients has a significantly increased risk of death (Brohi et al., 2003). Early identification of these patients enables timely access to the resources required, and has the potential to improve survival in these time-critical patients. Incorrect decisions will not only compromise survival but may also impact the potential for successful limb salvage.

Clinical markers of tissue perfusion, including blood gas analysis results, may be available within this time frame. However, these decisions are normally made without any objective evidence of the patient's risk of coagulopathy or death. Laboratory coagulation test results are not available within a useful time frame (Davenport et al., 2011) and accurate mortality predictions require information that is also not immediately available.

Within the same time frame, it must be decided whether the limb injury is contributing to the life threat. This is based on clinical signs of major haemorrhage from the limb. In these patients emergency haemorrhage control is indicated. Emergency haemorrhage control may necessitate procedures that jeopardise the potential for limb salvage, for example vessel ligation or prolonged tourniquet application, while other life-threats are managed.

Decision Two: Is the limb's vascular supply compromised?

Once management of life-threatening injuries is underway, the next priority is to decided whether the injured limb requires reperfusion. The duration of limb ischaemic is critical to salvage and one of the few variables that the treating team has some control over. Early identification of injuries resulting in vascular compromise will enable timely reperfusion and improve the potential for limb salvage. Clinical examination, ankle brachial pressure index measurements, and computerised tomographic angiography will usually provide sufficient information for accurate decision-making.

Decision Three: Is the limb viable?

During the initial operative evaluation of lower limb injuries, the surgeon needs to make decisions regarding the viability of the remaining tissues. Clinically non-viable tissue is debrided. As wounds are evolving, an assessment of the predicted viability of remaining tissues is made. Surgeons, and their patients, should use this operative information to make decisions on whether to pursue limb salvage or proceed with amputation. Operative

evaluation of severe lower limb injuries should occur within 24 hours of injury and definitive management decisions should be made soon thereafter, ideally within 72 hours (NICE, 2016).

Decision Four: Does sufficient functional tissue remain?

Finally, the treating team need to decide whether the reconstructed limb has the potential to provide a better functional outcome than an amputation with prosthesis would achieve. This requires an assessment of the functional capacity of the remaining healthy tissue together with an assessment of the patient's preference. These decisions should be made as soon as possible after injury, usually within the first few days, because delayed amputation decisions, either because of a passive decision-making strategy or following prolonged attempts at unsuccessful limb salvage, are associated with significant physical and mental morbidity, and mortality (Bondurant et al., 1988).

1.4 Decision-Support for Severe Lower Limb Trauma

1.4.1 Background to the Severe Lower Limb Trauma Decision-Support Tools

In an attempt to assist surgeons with the complex decision-making, a number of scores have been developed to differentiate the group of patients that will benefit from limb salvage from those in whom limb salvage attempts may be harmful and likely futile (table 1.4). These scores combine a number of prognostic factors to enable the categorisation of an individual patient into the most appropriate management pathway (table 1.5).

Table 1.4: Predictive scores to assist surgical management decisions in patients with severe lower limb trauma.

Reference	Predictive Score	Acronym
Gregory et al. (1985)	Mangled Extremity Syndrome Index	MESI
Howe et al. (1987)	Predictive Salvage Index	PSI
Johansen et al. (1990)	Mangled Extremity Severity Score	MESS
Russell et al. (1991)	Limb Salvage Index	LSI
McNamara et al. (1994)	Nerve injury, Ischaemia, Soft tissue injury, Skeletal injury, Shock, Age	NISSSA
Krettek et al. (2001)	Hanover Fracture Scale	HFS '98
Rajasekaran et al. (2006)	Ganga Hospital Score	GHS

Table 1.5: Prognostic factors utilised by the lower limb predictive scores.

Prognostic Factor	MESI	PSI	MESS	LSI	NISSSA	HFS '98	GHS
Patient Factors							
Age	X		X		X		X
Co-morbidities	X						X
Injury Factors							
Mechanism of injury	X		X		X		
Injury Severity	X						X
Limb injury factors							
Arterial injury	X	X	X	X	X	X	
Level of arterial injury		X					
Venous injury	X			X			
Skeletal injury	X	X	X	X	X	X	X
Soft tissue injury	X	X	X	X	X	X	X
Nerve injury	X		X	X	X	X	X
Complications							
Shock	X		X		X	X	X
Duration of ischaemia	X	X	X	X	X	X	
Wound contamination			X			X	X

MESI, Mangled Extremity Syndrome Index; PSI, Predictive Salvage Index; MESS, Mangled Extremity Severity Score; LSI, Limb Salvage Index; NISSSA, Nerve injury, Ischaemia, Soft tissue injury, Skeletal injury, Shock, Age; HFS '98, Hanover Fracture Scale; GHS, Ganga Hospital Score.
X: Prognostic Factor included in score or score was developed for injuries with this prognostic factor present.

1.4.2 Severe Lower Limb Trauma Predictive Scores

Mangled Extremity Syndrome Index (MESI)

Proposed by Gregory et al. (1985).

Aim: To develop a simple grading system to objectively assess the severity of an extremity injury and identify, at initial evaluation, the functionally salvageable versus the probably unsalvageable extremity.

Setting: Single US level-1 trauma centre: Eastern Virginia Medical School

Study population: Adults and children with upper- or lower-extremity trauma involving significant injuries to at least 3 of the 4 major limb tissues (integument, nerve, vessels or bone). Traumatic amputations excluded.

Outcome definition: Limb salvage or amputation (primary or secondary). Duration of follow-up not reported.

Development: Retrospective analysis of data from 17 patients with mangled extremities, five patients had upper-extremity injuries and some had multiple extremity injuries. Seven patients had their limbs salvaged and ten underwent amputation. Ten clinical variables 1) Age, 2) co-morbidities, 3) Injury severity, 4) shock, 5) ischaemic time, 6) skeletal injury, 7) arterial injury, 8) venous injury, 9) nerve injury and 10) integument injury, were selected as predictors based on what the authors believe to be pertinent to prognosis. The predictors were catagorised and a point score, increasing with increasing risk, attached to each category. The MESI score is a summation of these ten scores. A score of > 20 is suggested as predictive of the need for amputation.

Validation: No validation was performed.

Authors' conclusion: MESI may be useful in identifying patients, at initial evaluation, with functionally salvageable limbs or limbs that require amputation.

Predictive Salvage Index (PSI)

Proposed by Howe et al. (1987).

Aim: To identify all variables that might influence the ultimate outcome of combined vascular and orthopaedic injuries of the lower-extremity and develop a predictive score using these variables.

Setting: Single US level-1 trauma centre: Wake Forest University Medical Centre, North Carolina.

Study population: Adults with combined orthopaedic and vascular trauma of the lower-extremity.

Outcome definition: Limb salvage or amputation (primary or secondary). Duration of follow-up not reported.

Development: Retrospective analysis of data from 21 injured limbs. Twelve limbs were salvaged and nine limbs were amputated. Four clinical variables 1) level of arterial injury, 2) degree of bone injury, 3) degree of muscle injury and 4) ischaemic time, were identified by univariate analysis and included as predictors in the index. The predictors were catagorised and a point score, increasing with increasing risk, attached to each category. The PSI score is a simple summation of these four scores. In the development cohort, a score of ≥ 8 had a sensitivity of 78 percent and a specificity of 100 percent for predicting the need for amputation.

Validation: The authors did not validate their score.

Authors' conclusion: The PSI score may prevent surgeons from attempting to salvage a doomed or useless lower-extremity. This may permit earlier prosthetic rehabilitation after definitive primary amputation.

Mangled Extremity Severity Score (MESS)

Proposed by Johansen et al. (1990).

Aim: To develop and validate a simple and accurate prognostic score using objective clinical criteria that can discriminate between salvageable lower limb injuries and those that warrant amputation.

Setting: Two US level-1 trauma centres: Harborview Medical Centre and Tampa General Hospital.

Study population: Open fractures of the lower-extremity with associated vascular compromise. Patients with a transection of the sciatic or posterior tibial nerve were excluded as these injuries were regarded as an absolute indication for primary amputation.

Outcome definition: Limb salvage or amputation (primary or secondary). Patients were followed-up for 18 months after injury.

Development: Retrospective analysis of data from 26 injured limbs. Seventeen limbs were salvaged and nine limbs were amputated. Four clinical variables 1) skeletal/soft tissue injury, 2) limb ischaemia, 3) shock and 4) age, were selected as predictors based on what the authors believe to be pertinent to prognosis. They emphasise the selection of objective clinical criteria available early in the hospital course. The predictors were catagorised and a point score, increasing with increasing risk, attached to each category. The MESS score is a simple summation of these four scores. A score of ≥ 7 is suggested as predictive of the need for amputation. The authors acknowledge that this cut-off threshold is dependent on available technology and expertise.

Validation: The score was internally validated using the development cohort and an additional form of temporal validation was performed using a second, prospectively collected, cohort combining subsequent patients at the same institution and patients from a different level-1 trauma centre. The prospective analysis consisted of data from 26 injured limbs. Fourteen limbs were salvaged and twelve limbs amputated. All salvaged limbs had a score of 6 or less, and all amputations, 7 or more. Accuracy is reported as 100 percent. The authors assessed discrimination by comparing the mean MESS scores for salvaged and amputated limbs using an unpaired students t-test. A statistically significant ($p<0.001$) difference between mean scores in both arms of the study exists.

Authors' conclusion: MESS may be useful in selecting patients whose lower-extremity injuries warrant amputation.

Limb Salvage Index (LSI)

Proposed by Russell et al. (1991).

Aim: To develop an objective index that will assist surgical decisions during the initial and operative evaluation of severe lower-extremity injuries by predicting which patients would benefit from limb salvage and which should undergo early amputation.

Setting: Single US Level-1 trauma centre: Erlanger Medical Centre, Tennessee.

Study population: Adults and children with lower-extremity arterial injuries. Half the population had a blunt mechanism of injury and the other half penetrating. Traumatic amputations were excluded.

Outcome definition: Limb salvage or amputation (primary or secondary). Patients whose limbs were salvaged but underwent elective amputation for functional indications were included as amputations.

Development: Retrospective analysis of data from 70 injured limbs. Fifty-one limbs were salvaged and 19 amputated. Seven prognostic variables 1) Arterial injury, 2) Nerve injury, 3) skeletal injury, 4) skin injury, 5) muscle injury, 6) venous injury and 7) ischaemic time, were identified by univariate analysis and included as predictors in the index. The predictor variables were catagorised and a point score, increasing with increasing risk, attached to each category. Ischaemic time was weighted by having the most categories. The LSI is a summation of these seven scores. A score of ≥ 6 is suggested as an absolute indication for amputation.

Validation: The index was internally validated using the development cohort. All salvaged limbs had a score of 5 or less, and all amputations, 6 or more. The authors assessed performance by comparing the mean (student's t-test) and median (Mann-Whitney U test) LSI scores for salvaged and amputated limbs. The differences were statistically significant. The correlation between outcome and LSI score was calculated using the Pearson correlation co-efficient.

Authors' conclusion: The LSI is a valuable objective tool for the evaluation of severe limb injuries that can accurately identify patients that would benefit from limb salvage.

Nerve injury, Ischaemia, Soft tissue injury, Skeletal injury, Shock, Age (NISSSA)

Proposed by McNamara et al. (1994).

Aim: To modify the MESS score so as to improve the predictive performance for patients with open tibial fractures.

Setting: Single US Level-1 trauma centre: Medical Centre Hospital, San Antonio, Texas.

Study population: Adults and one child with open tibial fractures graded as type IIIB or IIIC according to the classification system of Gustilo and Anderson (Gustilo et al., 1984).

Outcome definition: Salvage or amputation (primary or secondary). Patients with salvaged limbs were followed-up for an average of 21.6 months.

Development: Retrospective analysis of data from 24 injured limbs. Thirteen limbs were salvaged and eleven amputated. Six clinical variables 1) Nerve injury, 2) Ischaemia, 3) Soft tissue injury, 4) Skeletal injury, 5) Shock and 6) Age, were selected as predictors based on a stepwise logistic regression analysis of individual variables. This represents a modification of the MESS score by adding a nerve injury variable and separating the MESS skeletal/soft tissue variable into its components to give them greater weight in the score. The predictor variables were catagorised and a point score, increasing with increasing risk, attached to each category. The NISSSA score is a summation of these six scores (range 0 – 19). A score of ≥ 9 is the optimal threshold for predicting the need for amputation.

Validation: Performance was assessed on the development cohort. Treating surgeons were not aware of score results. At the optimal threshold of NISSSA score ≥ 9, sensitivity was 82 percent and specificity 92 percent with a positive predictive value of 90 percent.

Authors' conclusion: Modification of the MESS score to the NISSSA score resulted in improved performance at predicting amputation in severe open tibial fractures.

Hanover Fracture Scale (HFS '98)

Proposed by Krettek et al. (2001).

Aim: 1) To modify an existing extremity salvage score, the Hanover Fracture Scale 1983, to include only variables with prognostic significance that are available during initial operative debridement. 2) To validate the modified score.

Setting: Single Specialist Trauma Centre: Unfallchirurgische Klinik, Hannover, Germany.

Study population: Adults with open long-bone fractures of upper and lower limbs.

Outcome definition: Primary amputation was defined as an amputation occurring within 48 hours of injury and secondary amputation occurring after this. Only primary amputation predictive performance was validated.

Development: Retrospective analysis of data from 182 injured limbs. Twenty limbs were amputated (eleven primary amputations) and 162 salvaged. Eight clinical variables: 1) Bone loss, 2) Periosteal stripping, 3) skin injury, 4) Muscle injury, 5) Limb Neurology, 6) Wound contamination, 7) Ischaemic time and 8) shock, were selected as predictors based on a multivariate analysis of variables from the original score and additional variables which included shock, periosteal stripping and AO classification. The level of significance for consideration was $p < 0.05$. The predictor variables were catagorised and a point score, increasing with increasing risk, attached to each category. The HFS '98 score represents a summation of these eight scores (range 0 – 22). Using a Receiver Operating Characteristic (ROC) analysis, a score of ≥ 11 was calculated as the optimal threshold for predicting amputation.

Validation: The score's performance was temporally validated on a prospective dataset of 87 limb injuries from the same centre. Seventeen limbs were amputated (twelve primary amputations) and 70 salvaged. At the optimal threshold score, sensitivity was 82 percent, specificity 99 percent, positive predictive value 99 percent, negative predictive value 96 percent and accuracy 97 percent.

Authors' conclusion: HFS '98 is a reliable extremity salvage score for all open long-bone fractures.

Ganga Hospital Score (GHS)

Proposed by Rajasekaran et al. (2006).

Aim: To develop a score for the prediction of limb salvage or amputation in patients with Gustilo type III A and B injuries.

Setting: Single Specialist Trauma Centre: Ganga Hospital, Coimbatore, India.

Study population: Adults and children with open tibial fractures graded as type IIIA or IIIB according to the classification system of Gustilo and Anderson (Gustilo et al., 1984).

Outcome definition: Salvage and amputation (primary and secondary). Patients with salvaged limbs were followed-up for an average of 43 (36 – 60) months.

Development: Retrospective analysis of data from 109 injured limbs. Seven limbs were amputated and 102 salvaged. Four clinical variables: 1) skin injury, 2) skeletal injury, 3) functional tissue (muscle and nerve) injury and 4) co-morbidity, were selected as predictors based on what the authors' believe to be pertinent to prognosis. The predictor variables were catagorised and a point score, increasing with increasing risk, attached to each category. The GHS score is a summation of these four scores (range 0 – 29). A GHS score of ≥ 14 was calculated, using a Receiver Operating Characteristic (ROC) analysis, as the optimal threshold for predicting amputation. At this threshold the models predictive performance on the development data was a sensitivity of 98 percent, specificity 100 percent, positive predictive value 100 percent, negative predictive value 70 percent and Area Under the Receiver Operator Characteristic curve (AUROC) of 0.998.

Validation: GHS predictive performance on the development data was compared to the performance of the MESS score and the Gustilo classification on the same data. A binary logistic regression analysis, with amputation as the dependent variable, and the three scores as the independent variables, showed that the GHS score was independently associated with amputation.

Authors' conclusion: The GHS is a practical score that may assist surgeons make appropriate decisions by predicting in which patients salvage will be successful and which will undergo amputation.

1.4.3 Critique of the Predictive Scores

Prognostic model development

Study population: The lower-extremity prognostic models were developed to predict outcomes in patients with lower extremity vascular injuries (LSI), orthopaedic injuries (HFS '98, GHS) and combined vascular/orthopaedic injuries (MESI, PSI, MESS, NISSSA). The majority of scores were developed using information from injured children and adults. Two studies (MESI, HFS '98) included patients with injuries to both the upper and lower extremities in their development populations, despite the criteria for reconstruction or amputation of upper and lower extremities being entirely different (Tintle et al., 2010a).

Study design: All seven prognostic models were developed by retrospective analysis of clinical data. The accuracy of this information and amount of missing data may affect the reliability of study results.

Sample size: The power of a prognostic model study depends on the number of observed events and not the number of patients (Altman, 2009). To overcome problems associated with multiple comparisons in the selection of variables and over-fitting the model to the development data, it is suggested that the number of observed events should be at least five to ten times the number of prognostic factors in the model (Peduzzi et al., 1995, Vittinghoff and McCulloch, 2007, Moons et al., 2009). None of the lower-extremity models achieved this. Observed events (amputations) ranged from seven to nineteen, yet none of the scores contained less than four variables. Sample size is therefore a major source of unreliability in these studies.

Setting: All models were developed at specialist trauma centres. This performance bias may impact the generalisability of the models. To overcome this, the MESS authors

suggested the model threshold might need to be adjusted according to available expertise and resources.

Selection of prognostic factors: No study described how potential prognostic factors were identified. Three studies did not describe any method of selecting prognostic factors (MESI, MESS, GHS) and factors included in these models may have been selected based on the authors' opinions. Prognostic factors were selected by univariate analysis (PSI, LSI) and multivariate analysis (NISSSA, HFS '98) for two models respectively. All models catagorised prognostic factors. In the majority of cases this was based on pragmatic rather than prognostic criteria. Furthermore, subjective descriptions were used to define categories for many factors.

Outcome: All scores were developed to predict primary and secondary amputations. The prediction of primary amputations is, however, flawed because the outcome, should salvage have been attempted, is not known. Four studies (MESI, PSI, LSI, HFS '98) did not report the duration of followed-up for salvaged limbs. Without adequate duration of follow-up it is possible that some limbs, regarded as successfully salvaged, required eventual amputation for functional reasons.

Model performance: The authors of the MESI score did not analyse their models predictive performance. In the other scores model performance was assessed on the development cohort.

Prognostic model validation

Only the MESS and HFS '98 authors validated the performance of their model on patient data not used in the development process. The statistical methods used to validate the MESS are not recognised methods of assessing model performance.

1.4.4 External Validity of the Predictive Scores

The severe lower limb trauma predictive scores were developed to assist surgeons with the complex decisions on the most beneficial management of these injuries. The most important information on the clinical usefulness of a predictive score is the validation of the scores performance on patient data that was not used in the development process. An ideal score would have a high sensitivity (accurate identification of patients that will benefit from amputation) to avoid prolonged and potentially harmful attempts at limb salvage, a high specificity (accurate identification of patients that will benefit from limb salvage) to avoid unnecessary amputation, and an AUROC of 1 (perfect accuracy) when applied to any population of patients with severe lower limb injuries.

A number of investigators have externally validated the lower-extremity predictive scores. These studies consistently show that the scores perform poorly on external patient data (Bonanni et al., 1993, Bosse et al., 2001, Brown et al., 2009, Dagum et al., 1999). Furthermore, the scores are unable to predict the functional recovery of patients that undergo limb reconstruction (Durham et al., 1996, Ly et al., 2008).

1.5 Aims and objectives

The overall aim of this thesis was to improve the understanding of decision-making following severe lower limb trauma, and develop accurate prognostic tools that can help identify those patients whose limb can be safely and effectively salvaged, and also identify those for whom attempts at limb salvage would be dangerous or fail. The long-term goal is that these tools will be used to support informed and evidence-based decisions, and thereby improve the quality of care and outcome from these devastating injuries. Specifically, the research objectives were:

1) To describe contemporary surgical decision-making in patients with severe lower limb trauma, and determine the rationale for, and characteristics of, these decisions.

2) To develop and validate an evidence-based prognostic model that can identify those patients who would benefit from immediate life-saving intervention, and those that may be harmed by attempts at definitive limb reconstruction.

3) To develop and validate an evidence-based prognostic model that can accurately predict the outcome of limb salvage in terms of viability.

CHAPTER TWO

Clinical Decision Support

2.1 Surgical Decision Making

Good judgement and sound decision-making are essential to safe and effective surgical practice (Yule et al., 2006). However, surgical decisions are often made under challenging conditions that may affect the accuracy of judgement. This is especially true for trauma and emergency surgery, where inadequate information, high degrees of uncertainty, critical time constraints, and high levels of risk, are common (Hirshberg and Mattox, 2004).

Naturalistic Decision-Making (NDM) is the science of studying how experts make decisions in these demanding, real-world situations (Zsambok and Klein, 2014). Using NDM concepts, two key stages in surgical decision-making have been identified. These are: 1) Situation assessment and 2) Choosing a course of action (Flin et al., 2007).

Situation assessment, or situational awareness, is a cognitive process that involves continuous perception and comprehension of the environment, thereby allowing potential problems to be recognised and defined (Rousseau et al., 2004). This includes diagnosing problems, assessing the level of risk the problem poses, estimating the time available to solve the problem, and identifying possible solutions. Accurate identification of potential problems is paramount to good surgical judgement, and misinterpreting the situation during this stage of decision-making is the most common cause of surgical errors (Way et al., 2003).

Once a problem is identified, the next stage is to decide on an appropriate course of action or treatment. If the situation is interpreted correctly, then decisions on appropriate action have a much greater chance of being correct too (Croskerry, 2013).

Theoretically, the decision-making stage is thought to involve two predominant processes of reasoning (Evans, 2003, Kahneman, 2011). Type 1 processes are fast, automatic, and based on learnt pattern recognition (Klein, 1993). While type 2 are slower, conscious,

analytical processes that require cognitive ability. Effective type 2 reasoning usually consists of a sequence of logical steps (Table 2.1).

Table 2.1: Key steps for good analytical decision-making (HBS, 2013)

Step 1	Define the problem including the risks and timeframe available for decisions (situational awareness).
Step 2	Establish clear objectives.
Step 3	Identify possible alternative solutions.
Step 4	Evaluate risks and benefits of the available alternatives.
Step 5	Determine the strategy most likely to achieve objectives.

Other methods of decision-making also exist (Flin et al., 2007). Rule-based decision-making involves identifying the situation, followed by looking-up, or remembering, the action specified in an appropriate guideline or standard operating procedure. A fourth strategy is creative decision-making, whereby a novel solution is devised for an unfamiliar problem.

Depending on the situation, experienced surgeons generally use pattern recognition (type 1) or analytical (type 2) decision-making strategies (Pauley et al., 2011). Simple decisions, that are familiar to the surgeon, are made using type 1 processes, while complex decisions, that require comparison of multiple options with similar risks and benefits, are made using type 2 reasoning. Junior clinicians frequently use rule-based decision-making, however, with repetition the actions are learnt, and become automatic pattern-recognition (Type 1) processes. Creative decision-making is rarely used in clinical surgery due to the risks and time constraints involved (Flin et al., 2007, Pauley et al., 2011).

2.2 Difficult decisions

What determines the difficulty of decision-making is the way the alternatives relate (Chang, 2014). When one alternative is better than the others, decision-making is straightforward and a rational decision can be made. Using a logical decision-making process maximises the chance of being able to make a rational choice. When it is unclear which alternative is better, or when neither alternative is better than the other, then decision-making becomes difficult.

Difficult decisions, where the best option is uncertain, may be the result of a number of vulnerabilities in the decision-making process. In particular, making decisions with uncertain or incomplete information, or not establishing clear objectives, may impede good judgement. In addition, a decision maker may not be able to accurately estimate the risks and benefits of alternatives to allow comparisons, or have difficulty communicating these estimates to colleagues, and the patient, to allow informed and shared decision-making. Each of these elements of the decision-making process provides important targets for future decision-support research.

The second situation, when neither alternative is better than the other, is a true difficult decision. Ruth Chang describes this as when two options are neither better, worse, nor equal to each other in value, but rather they are on a par (Chang, 2002). For example, two options for treating a limb injury may result in the same degree of disability, but a different kind of disability, and neither option is better than the other. A rational choice means an attempt is made to choose the best option. If the options are on a par, then a rational choice is not possible. In these situations, only the patient can decide which option best suits their needs and values. As clinicians in these situations, it is important

that we are able to communicate the implications of each option clearly, to allow the patient to make the most informed decision possible.

2.3 Uncertainty

"Medicine is a science of uncertainty and an art of probability"

(Sir William Osler)

Uncertainty is defined as the state of being uncertain, and refers to a circumstance where a present or future state, event, or outcome is not known, not definite, or not able to be relied upon. Medical information is inherently uncertain. Patients cannot describe exactly what they experience. Clinicians cannot interpret exactly what they observe. Diagnostic tests report with some degree of error, and medical research can only estimate the truth. Medical knowledge does not completely explain how the human body behaves, both normally and when injured, and patients may have variable responses to treatment. Moreover, nobody can precisely determine prognosis. As a result of this imperfect information, the true state of a patient, and the best treatment for a patient, are never completely certain. Uncertainty is thus a fundamental feature of medical decision-making (Sox et al., 2013).

It is essential that clinicians are able to understand and reason with uncertainty (Sox et al., 2013). Good clinical judgement is necessary to make accurate decisions using uncertain information and to recognise when uncertainty needs to be reduced to a point where a decision can be made. One approach to reducing uncertainty is to delay decision-making, allowing time for the situation to evolve and more reliable information to become available. Another approach is to gain additional information by performing further tests.

Although these approaches may make decision-making simpler by reducing uncertainty, they may also expose the patient to further harm, especially in emergency situations. Weighing up these risks and benefits is not straightforward.

Patients are also increasingly active in decisions about their care. The UK governments "no decision about me, without me" vision, aims to make shared decision-making between clinicians and patients the norm in the National Health Service (Coulter and Collins, 2011). To make this a reality, clinicians will need to be able to communicate uncertainty in a way that patients can understand and reason with, to enable informed decisions. However, both patients and clinicians are uncomfortable reasoning with uncertainty (Ofri, 2013). This is understandable, as medicine is taught, and expected to be, an exact science, with verified facts and definitive conclusions. In addition, communicating and reasoning with uncertainty generates a number of problems. Uncertainty is usually expressed in words or statements. For example, the likelihood of an uncertain state or outcome may be communicated in terms such as "I think that...", "it is likely that...", "there is a chance that...", or "it is possible that...". These words and statements are imprecise, and make understanding and reasoning with them difficult (Sox et al., 2013, Tversky and Kahneman, 1974). Furthermore, similar phrases may be used to communicate quiet different degrees of uncertainty (Bryant and Norman, 1980). This problem becomes even more complicated when a clinician tries to communicate changes in the degree of uncertainty, as new information becomes known (Sox et al., 2013).

Intuitive reasoning with uncertainty is also prone to cognitive biases (Tversky and Kahneman, 1974). This is because people naturally rely on a limited number of practical, but imperfect, problem solving techniques to make judgements under uncertainty. Although these techniques can be useful, they may also lead to systematic and serious judgement errors (Kahneman, 2011, Gigerenzer, 2002).

Despite the rapid expansion in medical knowledge, clinical decisions will continue to be based on uncertain information. The remainder of this chapter describes methods to understand, communicate, and reason with uncertainty and how these methods can be used to reduce judgement errors and support rational decision-making.

2.4 Probability

The Oxford English Dictionary (2015) defines probability as a measure of the extent to which something is likely to happen or be the case. It is expressed as a continuous number between zero and one, and allows any degree of uncertainty to be specified on this scale. Notably, probability may apply to the present state of a patient or the future state of a patient. The higher the number, the more certain we are that the state is present or will occur, with a probability of one representing absolute certainty. The lower the number, the more certain we are that the state is absent or will not occur, with a probability of zero representing an impossible event.

Probability is key to understanding, communicating, and reasoning with uncertainty (Sox et al., 2013). It provides a language that allows the degree of uncertainty to be quantified and expressed precisely, thus overcoming the ambiguity associated with words and phrases. By being able to express uncertainty precisely, it becomes possible to measure the effect of new information and adjust our belief accordingly. Probability therefore provides a framework that enables reasoning with uncertainty (Sox et al., 2013).

While probability may overcome many of the fundamental difficulties inherent to reasoning with uncertainty, it does not solve them all. Accurately estimating probabilities can be confusing and difficult, even for experienced clinicians (Casscells et al., 1978,

Gigerenzer and Edwards, 2003). In particular, intuitive probability estimates are prone to cognitive bias and errors (Tversky and Kahneman, 1974).

Published evidence, such as prevalence estimates, or the frequency of an event in a population, provides a more objective source of information for initial probability estimates than intuition (Sox et al., 2013). However, published evidence is not without limitations (Greenhalgh, 2014). The most important limitations affecting probability estimates from published evidence are selection bias and the generalisability of findings to the person or population of interest. Furthermore, published evidence can be reported in ways that are confusing to apply directly to probability estimation, which can also result in errors (Gigerenzer and Edwards, 2003).

In most real world problems, multiple factors will influence the probability of an event. Calculating probabilities, while taking into account the joint effects of multiple factors, is extremely difficult, and possibly beyond normal human mental ability (Fenton and Neil, 2012b). Fortunately, mathematics and computer technology can be used to accurately and reliably estimate probabilities and may help to prevent estimation errors.

2.5 Bayes Theorem

Bayes theorem is a simple, yet powerful, equation that allows initial probability estimates to be precisely updated when new evidence becomes available. The theorem was deduced by the minister and mathematician, the Reverend Thomas Bayes (1701 – 1761), and was published posthumously in 1763 (Bayes and Price, 1763). The theorem is stated as:

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

Where A is the event of interest and B the new evidence. P(A) and P(B) are the probabilities of events A and B independent of each other. P(A|B) is the conditional probability of event A given B, and P(B|A) is the conditional probability of B given A.

The theorem demonstrates how a prior belief about the probability of an event should change to account for new evidence.

This is best explained with an example. Suppose that the prevalence of serious injury in a population of deployed soldiers is three percent. In the same population, approximately 20 percent of soldiers don't wear their protective body armour. By examining the combat hospital records, it is discovered that two thirds of seriously injured soldiers were not wearing body armour. Military leaders would like to know the probability of a soldier suffering a serious injury, if they do not wear their body armour.

Answering this simple question with the available information is actually quite difficult, but this probability can easily be calculated using Bayes theorem.

Let S represent the event 'serious injury' and B represent 'no body armour'. Then the probability of suffering a serious injury when body armour is not used can be calculated as:

$$P(S|B) = \frac{P(B|S)P(S)}{P(B)} = \frac{0.66 \times 0.03}{0.2} \cong 0.1$$

In this example, Bayes theorem shows how our initial belief in the probability of serious injury increased from three percent to ten percent when we took into account new information that soldiers did not wear their body armour. This updated probability is termed the posterior probability, while the initial probability of three percent is termed the prior probability.

Bayes theorem provides a simple, consistent, and rational method to calculate probabilities while avoiding common errors associated with reasoning with uncertainty (Fenton and Neil, 2012b). It is an extremely powerful theorem. However, when Bayes theorem is applied to problems with multiple influential variables, the mathematical complexity increases exponentially, and these problems become exceedingly difficult and time-consuming to calculate (Spicer, 1980). Bayesian Networks were developed to overcome this problem.

2.6 Bayesian Networks

Bayesian Networks (BNs) are powerful mathematical models that enable accurate probability calculations, using Bayes theorem, in complex problems involving multiple influential variables.

2.5.1 Components of Bayesian Networks

BNs consist of two parts: 1) a network structure that graphically describes the models' variables and their relations, and 2) a set of parameters that captures the strength of the relationships between variables.

2.5.1.1 Network Structure

The network structure has two components: nodes and edges (Figure 2.1).

Nodes: Nodes represent the individual variables included in the model. Each node has a defined set of values or states that it may take. These values or states are determined by the variable the node represents and may either be discrete or continuous. Discrete nodes can be further catagorised into Boolean nodes, Labelled nodes, Ranked nodes, and discrete Numeric nodes. Boolean nodes take on exactly two states, such as True / False, or Present / Absent. Labelled nodes take on more than two states but have no inherent order, for example branches of the armed forces may be army / navy / air force. Ranked nodes take on more than two states but these states have an order, for example, mild / moderate / severe. Discrete numeric nodes can take on any whole number in a range of numbers. For example, a patient's age in years could be expressed as a number with a possible value between zero and 110.

An important rule in BNs is that discrete nodes must be defined by a set of mutually exclusive and collectively exhaustive states. This means the variable must take on exactly one of the defined states at any time.

Nodes may also represent numeric variables that are measured on a continuous scale (Neil et al., 2007). Using expert knowledge, it is often possible to apply logical constraints to a continuous node. For example, systolic blood pressure may be limited to a range between zero and 300 mmHg, as it is not possible to have a negative blood pressure and the maximum pressure a human heart can generate is approximately 300 mmHg.

Edges: Edges represent the relationship between variables (nodes). Two variables are connected by an edge if one of the variables has a direct effect on the other. The direction of the edge indicates the direction of the effect. In this way the network structure can indicate which variables are related, and just as important, which variables are not directly related. Variables can then be classified by their relationship to each other. If a directed edge connects two variables A and B, as in A → B, then A is a parent of B and B is a child of A. Similarly, in chains of variables, as in A → B → C, A is an ancestor of C and C is a descendant of A. Within this structure, a variable is dependant on the state of its parents and children but is conditionally independent of its non-descendants given its parents. An important constraint in the network structure is that the directed edges between nodes must not form a cycle, that is, it must not be possible to return to a node simply by following directed edges. For this reason the network structure of a BN is often called a Directed Acyclical Graph or DAG.

2.5.1.2 Parameters

Each node in a BN has an accompanying set of parameters that quantifies the relationship between that node and the nodes connected to it. These parameters are probability values assigned to each of the possible states of the variable that the node represents. The initial nodes in a BN do not have parent nodes. The probability value for each possible state of these initial nodes is estimated from the prior probability of the respective state occurring in the population. For example, a BN node may represent the variable gender, with the possible states defined as male or female. The probability of either of these states in the general population may be estimated at 0.5, or 50 percent. All other nodes in a BN have parent nodes. The probability value for each state of these nodes is defined, given every possible state of the parent nodes. This means that the probability distributions of all nodes with parent nodes are conditional on the state of the parent nodes. For discrete nodes, a probability value is set for each of the possible individual node states and a Node Probability Table (NPT) is constructed containing a set of all the possible probability values related to that node. The size of a given node's NPT depends on the number of states the node can take and the number of parent nodes the node has. Increases in these two factors result in an exponential increase in the NPT size. For continuous nodes, a statistical probability distribution is used. The statistical probability distribution has a range between zero and one and is characterised by its mean and variance.

2.5.2 Bayesian Network reasoning

Once the network structure and parameters have been defined, the BN can be used to calculate the probability of any variable in the modelled domain. Known information is entered into the BN and used to update the probabilities of unknown variables. This process uses Bayes Theorem and is termed propagation. The flow of information through the BN can be in any direction and is not limited by the direction of the edges. Furthermore, new information for any number of variables from any part of the BN

model can be entered, and propagation will be used to update the probabilities of all the unknown variables.

This process enables some powerful types of reasoning:

1. *Predictive (Causal) reasoning*: Predictive reasoning follows the direction of the edges, from cause to effect. Entering new information into a 'cause' node will update the probabilities in its 'effect' node. In the example BN fragment shown in figure 2.1, knowing that a soldier sustained a traumatic injury will increase the probability of receiving a blood transfusion or undergoing surgery.
2. *Diagnostic reasoning*: Diagnostic reasoning occurs in the opposite direction to the edges, from effect to cause. Entering known information into an 'effect' node will update the probabilities in its 'cause' nodes. In the example BN, knowing that a soldier underwent surgery will increase the probability that he/she was injured or developed appendicitis.
3. *Explaining away*: This reasoning occurs if there are two or more causes for an effect. If the effect is present, the probabilities of all the causes will increase (diagnostic reasoning). However, if one of the causes is known to be present, the probabilities of the other causes will decrease (explaining away). For example, if we know that a soldier required emergency surgery, knowing that they suffered a traumatic injury will make appendicitis less likely.
4. *Combined reasoning*: Within the BN, the above types of reasoning can be combined in any way to update the probability of unknown variables.

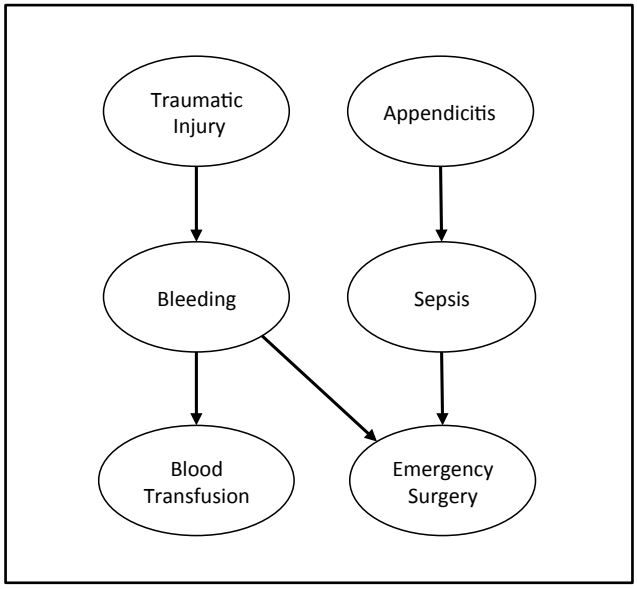


Figure 2.1: A simple Bayesian Network model showing possible reasons for needing emergency surgery.

2.5.3 Advantages of Bayesian Networks

BNs provide a number of additional, and unique, benefits that support good judgement and sound, evidence-based, decision-making.

Firs, the graphical structure of a BN allows all the variables and relationships in a domain to be clearly presented. BNs are therefore able to encode and reflect domain knowledge in a simple and coherent way. This explicit representation helps the user understand the reasoning process and what's more, it allows the reasoning process to be clearly communicated.

Second, a BN will update the probability distributions of unknown variables when any new information for any number of variables is entered. There is therefore no specific set of inputs that is required to calculate the probability of an unknown variable. Indeed, if no information is entered, the model simply assumes the prior probability distribution for each unknown variable. By contrast, traditional statistical techniques, such as regression modelling, require all of the independent variable inputs to be entered into the model

before the value of the dependant variable can be calculated. This ability to handle missing data is a major advantage of BNs over traditional techniques, especially when reasoning with uncertainty in emergency situations, where incomplete information is common.

Third, BNs provide a framework that allows a range of evidence to be combined and used to reason with uncertainty. Types of evidence include, but are not limited to, expert opinion, data, and published literature. This has beneficial implications for the generalisability of these models and evidence-based decision-making.

2.7 Summary

Good decision-making requires strong situational awareness and astute reasoning skills. For complex decisions, an analytical reasoning strategy that allows comparison of the risks and benefits of alternate solutions is necessary. Uncertainty is common, and rational decisions are difficult if the risks and benefits are uncertain. Probability provides a language that allows us to understand, communicate, and reason with uncertainty. While Bayes theorem and Bayesian Networks provide the tools needed to accurately estimate and update probabilities using available information and existing knowledge. Using these tools to accurately estimate the probability of uncertain risks and benefits has the potential to improve situational awareness and support rational and evidence-based decisions.

CHAPTER THREE

A Contemporary Analysis of Severe Lower Limb Trauma Decision-Making

3.1 Introduction

Deciding between amputation and salvage of a severely injured limb is one of the most difficult decisions a surgeon can face (Lange, 1989, Hansen Jr, 1989, Busse et al., 2007, Scalea et al., 2012). A clear understanding of the clinical reasoning behind these decisions, including the complex trade-off between estimated risks and benefits, is central to accurate decision-making (Hirshberg and Mattox, 2004, Sox et al., 2013, Kahneman, 2011). This fundamental knowledge, however, is poorly described and contributes to difficulties in making rational and timely decisions (NICE, 2016).

Lower limb trauma is the predominant injury in modern warfare and an important cause of preventable death and marked disability including limb loss (Owens et al., 2007, Owens et al., 2008, Eastridge et al., 2012, MacKenzie et al., 2005, Doukas et al., 2013). Surgical management of severe injuries is complex, with an array of resuscitation, reperfusion, and reconstruction strategies possible (Nanchahal J, 2009, Scalea et al., 2012, Schreiber, 2012, Glass et al., 2009). The aims of surgery are first to ensure survival and then to reconstruct the most functional limb or residual limb possible (Nanchahal J, 2009, Clasper, 2007).

Major advances in limb reconstruction have made salvage technically possible in all but the most severe injuries (Wagels et al., 2013, Whitaker et al., 2011). However, in some situations, prolonged attempts at limb salvage may be dangerous or result in outcomes that are worse than what an early amputation with prosthesis would achieve (Bondurant et al., 1988, Hansen Jr, 1989). Optimal patient outcome depends on sound surgical judgement and timely decision-making (Lange, 1989, Hansen Jr, 1989). But despite the considerable impact amputation/salvage decisions may have on health (Bosse et al., 2002, Doukas et al., 2013), there has been minimal progress understanding how to choose between them (Johansen and Hansen Jr, 2015).

A number of predictive scores have been developed to assist surgeons with these complex decisions (Johansen et al., 1990, Gregory et al., 1985, Russell et al., 1991, McNamara et al., 1994, Krettek et al., 2001, Rajasekaran et al., 2006). None, however, have been shown to provide any clinically reliable decision support or allow an accurate assessment of the risks that influence decisions (Bonanni et al., 1993, Bosse et al., 2001, Brown et al., 2009, Durham et al., 1996). Moreover, there are significant differences in experienced surgeons' beliefs regarding the most important factors influencing the decision to amputate or reconstruct injured lower limbs (MacKenzie et al., 2002).

A clear understanding of the rationale for amputation decisions will provide fundamental knowledge to support surgeons and their patients in making informed choices. This has the potential to improve the quality of care and outcomes from these devastating injuries.

3.2 Aims and objectives

The overall aim of this study was to analyse the decision-making of trauma surgeons treating casualties with major lower extremity vascular injuries.

The *first* objective was to determine what treatment decisions were made and the time frames these decisions were made in.

Second, to establish the rationale for these decisions.

T*hird*, to analyse the relationships between clinical characteristics and treatment decisions.

3.3 Methods

3.3.1 Study design and setting

This was a retrospective cohort study of US military servicemen who sustained lower extremity vascular injuries while serving in Iraq or Afghanistan between March 2003 and February 2012.

3.3.2 Study population

Potentially eligible participants were identified from the Global War on Terror Vascular Injury Initiative (GWOT-VII) database. GWOT-VII is a cohort study that maintains prospective follow-up of US military servicemen who sustained extremity vascular trauma while serving in the wars in Iraq and Afghanistan (Stannard et al., 2012). Cases are identified from the Joint Theatre Trauma Registry (JTTR), which is a comprehensive database of all injured casualties treated at US Military treatment facilities. Servicemen who sustained a vascular injury are identified from the JTTR using Abbreviated Injury Scale (AIS) and International Classification of Diseases, Ninth Revision (ICD-9) codes for vascular injury (arterial and venous) and vascular injury repair. Before inclusion in the GWOT-VII database, specially trained research nurses reviewed the corresponding military medical records to confirm vascular injury and JTTR data accuracy. Both registries are held and maintained by the United States Army Institute of Surgical Research (USAISR) at Fort Sam Houston, Texas. GWOT-VII was reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board. Informed agreement to undertake long-term follow-up, patient interviews, health-related quality of life surveys, and grant researchers access to relevant medical records, is obtained from patients enrolled in the initiative.

US servicemen who sustained a major lower extremity injury involving at least one named lower extremity artery, distal to the aortic bifurcation, were included in this study. Servicemen with iatrogenic vascular injuries, isolated venous injuries, and complete traumatic amputations were excluded.

Lower extremity vascular trauma (LEVT) was used as a representative population to study amputation / salvage decision-making for a number of reasons. First, these injuries pose a threat to the patients' life and the limbs viability, in addition to the risks posed by severe limb injuries without a vascular component. As a result, these injuries often require immediate intervention, and decisions regarding amputation and salvage are more common and generally more complex. Second, LEVT is associated with high amputation rates (Kauvar et al., 2011, Mullenix et al., 2006) and accurate decision-support may have the most utility in this population. Last, the population can be clearly defined allowing accurate analysis.

3.3.3 Data collection

Data on patient demographics, mechanism of injury, injury characteristics, injury severity scores, management, and outcome were extracted from the GWOT-VII database and the JTTR. This was supplemented and corroborated with additional information from the Armed Forces electronic medical records and patient interviews. Injury severity was classified by trained personnel according to the Injury Severity Score (ISS) (Baker et al., 1974) and Mangled Extremity Severity Score (MESS) (Johansen et al., 1990). Outcome data, including the timing of, and rationale for amputation were collected from operative records, clinic letters, and records of multi-discipline meetings.

3.3.4 Outcomes

The outcome of interest was the treatment decision in terms of limb salvage or major lower extremity amputation, and the rationale for these decisions. A major lower

extremity amputation was defined as an amputation above the level of the ankle. Primary amputation was defined as the surgical amputation of an injured limb at the first operative procedure and secondary amputation was defined as the surgical amputation of an injured limb as a secondary procedure following an initial attempt at limb salvage. For limbs that underwent amputation, additional outcomes included the timing of, and anatomical level of amputation. The timing of amputation was measured in days after injury. Secondary amputation was further catagorised as early (≤ 30 days after injury) and late (> 30 days after injury). For the purposes of this study, follow-up was complete up until 01 February 2013, one year after the end of the study period. This duration of follow-up has been suggested to be sufficient for lower extremity trauma research (Castillo et al., 2011).

3.3.5 Definitions

Arterial injuries were categorized into four zones according to the anatomical level of injury: iliac, including common and external iliac arteries; femoral, including common and superficial femoral arteries; popliteal arteries; and tibial arteries. Profunda Femoris injuries were considered as a separate group. Soft tissue injuries were catagorised by level (above-knee, knee, below-knee, and ankle/hindfoot) and degree of tissue injury. The degree of tissue injury was catagorised as none/minor (no tissue loss), moderate (≤ 25 percent tissue loss), and severe (> 25 percent tissue loss including partial traumatic amputations). Initial blood transfusion requirements were measured in units of blood (whole blood or packed red blood cells) transfused within 24 hours of injury (units blood/24 hours). A massive blood transfusion was defined as the transfusion of 10 or more units of blood (whole blood or packed red blood cells) within 24 hours of injury (Malone et al., 2006). The degree of shock prior to surgery was catagorised as normal (SBP always > 90mmHg, ≤ 2 units blood/24 hours), compensated (SBP transiently below 90mmHg, > 2 units blood/24 hours), or uncompensated (SBP consistently below 90mmHg, massive blood transfusion, coagulopathy).

3.3.6 Statistical analyses

Statistical analyses were performed using GraphPad PRISM v6 (GraphPad, La Jolla, CA, USA) and SPSS v20 (SPSS, Chicago, Il, USA). Normal-quartile plots were used to test for normality. Non-parametric data are reported as median with interquartile range (IQR) and categorical data as frequency (n) and percentage (%). The Mann–Whitney U test was used to compare numerical data and Fisher's Exact test was used to compare categorical data. Freedom from limb amputation was estimated using the Kaplan-Meier method (Kaplan and Meier, 1958). Univariate analysis was used to assess the association between patient and injury characteristics and the timing of amputation. Results are reported as a crude Odds Ratio (OR) with 95 percent Confidence Intervals (CI). Statistical significance was set as a two tailed p-value of < 0.001.

3.4 Results

Between 01 March 2003 and 01 February 2012, 576 US soldiers sustained lower extremity vascular injuries in battle and were included in the GWOT-VII registry. Nineteen soldiers were excluded as the injury resulted in a complete traumatic limb amputation, and three soldiers with iatrogenic vascular injuries were excluded. Of the remaining 554 soldiers, twenty-five sustained bilateral lower extremity vascular injuries. In total, we analysed the decision-making for 579 injured lower limbs.

3.4.1 Baseline characteristics

The 554 casualties had a median age of 23 (range: 18 – 54) years, and blast was the most common mechanism of injury (n=395, 68.2 percent). The baseline characteristics of the study population are presented in Table 3.1. Median duration of follow-up was 6.3 years, ranging from 345 days to 10.5 years.

3.4.2 Therapeutic decisions

Of the 579 injured limbs, salvage was attempted in 530 (91.5 percent) and 49 (8.5 percent) underwent primary amputation. Of the limb salvage attempts, 440 limbs (83.0 percent) were successfully salvaged and 90 limbs (17.0 percent) underwent secondary amputation. Overall, 139 injured lower limbs (24.0 percent) underwent amputation.

3.4.3 Timing of therapeutic decisions

All primary amputations were performed within 24 hours of injury. Secondary amputations were performed between one day and five years (1848 days) after injury. Two thirds of secondary amputations (60 limbs) were performed within 30 days of injury (early amputations), with 24 procedures (26.6 percent) performed within 72 hours of injury.

Table 3.1: Baseline characteristics of 554 soldiers with 579 injured lower limbs.

Characteristic	Missing Data (%)	Overall (n = 579)	Salvage (n = 440)	Amputation	
				Primary (n = 49)	Secondary (n = 90)
Age (range)	0	23 (18 – 54)	23 (18 – 54)	23 (19 – 46)	24 (19 – 44)
Mechanism of injury					
Blast	0	395 (68.2)	277 (63.0)	46 (93.9)	72 (80.0)
Blunt	0	18 (3.1)	14 (3.2)	0	4 (4.4)
Penetrating	0	166 (28.7)	149 (33.9)	3 (6.1)	14 (15.6)
Injury Severity					
Injury Severity Score	27 (4.7)	14 (10 – 22)	14 (10 – 18)	24 (17 – 33)	17 (11 – 24)
MESS	32 (5.5)	6 (5 – 7)	6 (5 – 6)	7 (6 – 8)	7 (6 – 7)
Arterial Injury [a]					
Iliac Artery	0	20 (3.5)	13 (3.0)	6 (12.2)	1 (1.1)
Femoral Artery [b]	0	182 (31.4)	139 (31.6)	19 (38.8)	24 (26.7)
Popliteal Artery	0	129 (22.3)	86 (19.5)	17 (34.7)	26 (28.9)
Tibial arteries	0	253 (43.7)	187 (42.5)	19 (38.8)	47 (52.2)
Profunda Femoris Artery	0	32 (5.5)	31 (7.1)	1 (2.0)	0
Multiple arterial injuries	0	35 (6.0)	15 (3.4)	9 (18.4)	11 (12.2)
Associated Limb Injuries					
Venous injury	0	246 (42.5)	181 (41.1)	26 (53.1)	39 (43.3)
Nerve injury	74 (12.8)	179 (35.4)	119 (31.6)	21 (50.0)	39 (44.8)
Fracture	20 (3.5)	320 (57.2)	191 (45.5)	48 (98.0)	81 (90.0)
Soft tissue injury [c]	132 (22.8)				
None / minor		105 (23.5)	102 (32.2)	2 (4.3)	1 (1.2)
Moderate		208 (46.5)	186 (58.7)	3 (6.5)	19 (22.6)
Severe		134 (30.0)	29 (9.1)	41 (89.1)	64 (76.2)
Complications					
Shock [d]	15 (2.6)				
None		265 (47.0)	231 (53.7)	7 (14.9)	27 (31.0)
Compensated		146 (25.9)	119 (27.7)	8 (17.0)	19 (21.8)
Uncompensated		153 (27.1)	80 (18.6)	32 (68.1)	41 (47.1)
Compartment syndrome	0	34 (5.9)	25 (5.7)	2 (4.1)	7 (7.1)
Ischaemic time > 6 hours	273 (47.2)	18 (5.9)	1 (0.4)	7 (35.0)	10 (20.8)
Arterial Repair	17 (2.9)				
Ligation		198 (35.2)	146 (34.3)	31 (63.3)	22 (25.3)
Primary repair		89 (15.8)	75 (17.6)	3 (6.1)	11 (12.6)
Interposition graft		267 (47.5)	205 (48.1)	8 (16.3)	54 (62.1)

Data presented as number (percent) or median (IQR) unless otherwise stated. [a] Percentages may not add up

to 100 percent as some patients had multiple vascular injuries. [b] Common and Superficial femoral artery. [c] None/minor = no tissue loss; Moderate = < 25 percent tissue loss; Severe = ≥ 75 percent tissue loss/ partial traumatic amputations/mangled extremities. [d] Compensated = Systolic Blood Pressure transiently below 90mmHg, > 2 units blood/24 hours; Uncompensated = Systolic Blood Pressure consistently below 90mmHg, massive blood transfusion, coagulopathy. MESS, Mangled Extremity Severity Score

One third of secondary amputations (30 limbs) were performed beyond 30 days of injury (late amputations), with sixteen procedures (11.5 percent of all lower limb amputations) performed more than one year after injury, and four amputations performed more than two years after injury. The probability of limb amputation increased rapidly in the first few days after injury (Figure 3.1) with a continued but more gradual increase beyond 30 days after injury (Figure 3.2).

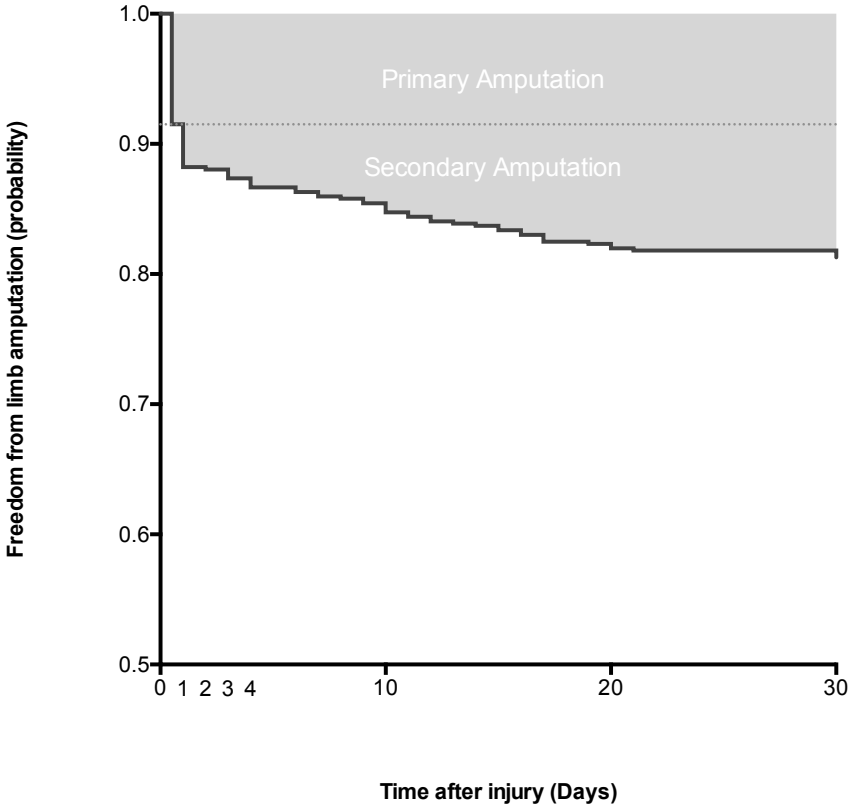


Figure 3.1: Kaplan-Meier estimates of freedom from limb amputation during the first 30 days following injury.

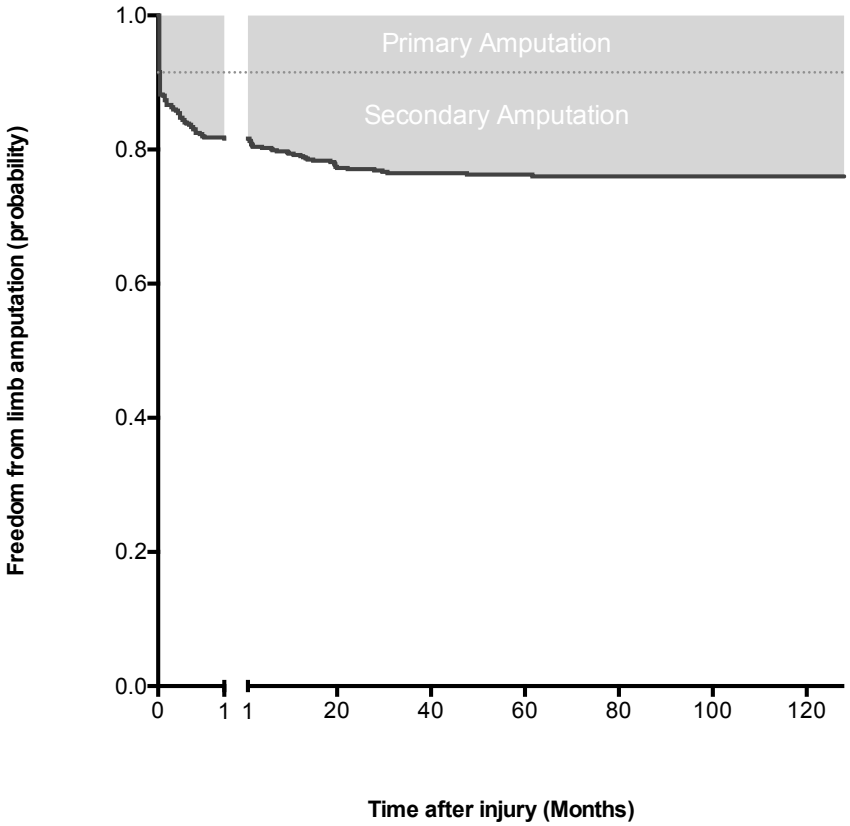


Figure 3.2: Kaplan-Meier estimates of freedom from limb amputation during the first ten years following injury.

3.4.4 The rationale for primary amputation

Forty-nine injured limbs (8.5 percent) underwent primary amputation and these procedures accounted for 35 percent of all amputations. The average age of patients undergoing primary amputation was 23 (range: 19 – 46) years, which was similar to the average age of those undergoing salvage or secondary amputation (Table 3.1). In univariate analysis, patients who underwent primary amputation were more likely injured by a blast mechanism (OR 8.25), had more severe limb injuries as evidenced by more frequent multiple level arterial injuries (OR 6.38), associated fractures (OR 57.55), and severe soft tissue injury (OR 72.10), and were more likely to have uncompensated haemorrhagic shock (OR 24.92) (Table 3.2). Although uncommon, delayed access to surgical revascularisation of ischaemic limbs was also strongly associated with primary amputation (OR 127.0).

The rationale for primary amputation was clearly documented in all cases (Table 3.3). Twenty-three limbs underwent primary amputation because there was insufficient tissue for limb (fifteen patients) or foot (eight patients) reconstruction. Nineteen limbs underwent primary amputation as part of resuscitation to save the patients life (Damage Control). And fourteen limbs underwent primary amputation because of non-viable limb tissue. Seven cases had more than one indication and the overlap is shown in Figure 3.3.

All 23 limbs (100 percent) that underwent primary amputation because there was insufficient tissue for limb reconstruction had severe soft tissue injuries (> 25 percent tissue loss) at the injured level, compared to eighteen of 26 limbs (69 percent) that underwent primary amputation for other reasons ($p = 0.005$).

All nineteen soldiers that underwent primary amputation for resuscitation had uncompensated haemorrhagic shock, including eight soldiers (42 percent) who suffered a period of traumatic cardiac arrest. By comparison, only thirteen of the 30 (43 percent) primary amputations performed for reasons other than resuscitation had uncompensated haemorrhagic shock ($p < 0.0001$) and none suffered a cardiac arrest. Soldiers that underwent primary amputation for resuscitation were transfused significantly more blood products (70 (IQR: 48 – 114) units vs. 22 (IQR: 8 – 47) units; $p < 0.0001$), including Packed Red Blood Cells (33 (IQR: 20 – 42) units vs. 9 (IQR: 5 – 28) units; $p = 0.0003$), during the first 24 hours following injury, than patients that underwent primary amputation for other reasons.

All fourteen limbs that underwent primary amputation for non-viable tissue had clearly non-viable tissue identified at first operative examination. Seven (50 percent) of these patients had a prolonged duration of ischaemia (> 6 hours) before surgical care. No cases

of prolonged ischaemia were identified in patients that underwent primary amputation for other reasons.

Table 3.2: Univariate analysis of factors associated with primary amputation.

Factor		Salvage (n = 440)	Primary Amputation (n = 49)	Univariate analysis Crude OR (95% CI)	p-value
Age (Range)		23 (18 – 54)	23 (19 – 46)	0.99 (0.95 – 1.04)	0.726
MOI	Penetrating	149 (33.9)	3 (6.1)	1.0	
	Blunt	14 (3.2)	0	-	-
	Blast	277 (63.0)	46 (93.9)	8.25 (2.52 – 26.97)	< 0.0001
Arterial injury site	Femoral	139 (31.6)	19 (38.8)	1.0	
	Popliteal	86 (19.5)	17 (34.7)	1.25 (0.58 – 2.70)	0.575
	Tibial	187 (42.5)	19 (38.8)	0.59 (0.28 – 1.25)	0.165
	Iliac	13 (3.0)	6 (12.2)	3.72 (1.25 – 11.07)	0.018
Multiple arterial injury		15 (3.4)	9 (18.4)	6.38 (12.62 – 15.49)	< 0.0001
Associated injury	Venous Injury	181 (41.1)	26 (53.1)	1.62 (0.90 – 2.93)	0.112
	Nerve Injury	119 (31.6)	21 (50.0)	2.16 (1.14 – 4.11)	0.019
	Fracture	191 (45.5)	48 (98.0)	57.55 (7.87 – 420.83)	< 0.0001
Soft tissue injury	None / minimal	102 (32.2)	2 (4.3)	1.0	
	Moderate	186 (58.7)	3 (6.5)	0.83 (0.35 – 5.00)	0.823
	Severe	29 (9.1)	41 (89.1)	72.10 (16.45 – 316.12)	< 0.0001
Shock	None	246 (69.7)	7 (14.9)	1.0	
	Compensated	68 (19.3)	8 (17.0)	3.15 (1.11 – 8.90)	0.031
	Uncompensated	39 (11.0)	32 (68.1)	24.92 (10.43 – 59.52)	< 0.0001
Compartment syndrome		25 (5.7)	2 (4.1)	0.71 (0.16 – 3.08)	0.643
Ischaemic time	> 6 hours	1 (0.4)	7 (35.0)	127.1 (14.5 – 1111.2)	< 0.0001
Arterial repair	Primary repair	75 (17.6)	3 (6.1)	1.0	
	Interposition graft	205 (48.1)	8 (16.3)	0.98 (0.25 – 3.78)	0.971
	Ligation	146 (34.3)	31 (63.3)	5.14 (1.52 – 17.38)	0.009

Data is presented as number (percent) and Odds Ratio (95 percent Confidence Interval) unless otherwise specified.
OR, Odds Ratio; CI, Confidence Interval; MOI, Mechanism Of Injury.

Table 3.3: Indications for amputation in 579 severely injured lower limbs. Indications are divided according to the timing of the decision to perform the amputation.

Primary Amputation	**(n = 49)**
Resuscitation (Damage Control)	19 (38.8)
Non-viable tissue	14 (28.6)
Insufficient tissue for functional reconstruction	15 (30.6)
Non-reconstructable foot	8 (16.3)
Secondary Amputation (Early)	**(n =60)**
Non-viable tissue	44 (73.3)
Infected tissue	21 (35.0)
Insufficient tissue for functional reconstruction	7 (11.7)
Resuscitation – Graft haemorrhage	2 (3.3)
Functional limitation	1 (1.6)
Unclear	2 (3.3)
Secondary Amputation (Late)	**(n = 30)**
Functional limitation	24 (80.0)
Chronic pain	15 (50.0)
Chronic infection	6 (20.0)
Non-healing wounds	3 (10.0)
Other	1 (3.3)
Data presented as number (percent). Percentages do not add up to 100 percent as some cases had more than one reason for amputation.	

3.4.5 The rationale for secondary amputation

Ninety injured limbs (17.0 percent) underwent secondary amputation following an attempt at limb salvage. These procedures accounted for 65 percent of all lower limb amputations.

Compared to patients with salvaged limbs, patients that underwent secondary amputation were more likely injured by a blast mechanism (OR 2.77), had more severe limb injuries as evidenced by more frequent multiple level arterial injuries (OR 3.95), associated

fractures (OR 10.79), and severe soft tissue injury (OR 54.29), and were more likely in uncompensated haemorrhagic shock (OR 4.39) (Table 3.4). Delayed access to surgical revascularisation of ischaemic limbs was again strongly associated with amputation (OR 28.83). Patients with a lower limb nerve injury had a small increase in risk of amputation (OR 1.76). Injury factors associated with secondary amputation were similar to those associated with primary amputation, however, the magnitude of the relationship was less for secondary amputations.

The rationale for secondary amputation was clearly documented for 88 injured limbs (97.8 percent) and are presented in Table 3.3. The main reasons for early secondary amputation were non-viable tissue (73.3 percent), infected tissue (35.0 percent), and insufficient tissue for functional reconstruction (13.3 percent). In many limbs there was more than one indication for amputation, the overlap between the key indications is shown in Figure 3.3.

The causes of non-viable tissue leading to secondary amputation were: failure of the revascularisation graft due to thrombosis (n = 27, 61.4 percent) or haemorrhage (n =1, 2.3 percent); progressive necrosis of the wound following initial operative debridement (n = 14, 31.8 percent); and iatrogenic complications (n =2, 4.6 percent). Ten soldiers who underwent secondary amputation because of a non-viable limb had a prolonged duration of ischaemia (> 6 hours) before surgical care. No cases of prolonged ischaemia were identified in patients that underwent secondary amputation for other reasons.

Late secondary amputations (30 limbs) were performed because of functional limitation (24 limbs, 80.0 percent), chronic pain (15 limbs, 50.0 percent), chronic infection (6 limbs, 20.0 percent), non-healing wounds (3 limbs, 10.0 percent), and following a second traumatic injury to a salvaged limb (1 limb, 3.3 percent).

Table 3.4: Univariate analysis of factors associated with secondary amputation.

Factor		Salvage (n = 440)	Secondary Amputation (n = 90)	Univariate analysis Crude OR (95% CI)	p-value
Age (Range)		23 (18 – 54)	24 (19 – 44)	1.00 (0.97 – 1.04)	0.936
MOI	Penetrating	149 (33.9)	14 (15.6)	1.0	
	Blunt	14 (3.2)	4 (4.4)	3.04 (0.88 – 10.50)	0.079
	Blast	277 (63.0)	72 (80.0)	2.77 (21.51 – 5.07)	0.001
Arterial injury site	Femoral	139 (31.6)	24 (28.9)	1.0	
	Popliteal	86 (19.5)	26 (24.4)	1.50 (0.79 – 2.83)	0.217
	Tibial	187 (42.5)	47 (52.2)	1.37 (0.79 – 2.37)	0.258
	Iliac	13 (3.0)	1 (1.1)	0.44 (0.06 – 3.51)	0.438
Multiple arterial injury		15 (3.4)	11 (12.2)	3.95 (1.75 – 8.91)	0.001
Associated injury	Venous Injury	181 (41.1)	39 (43.3)	1.09 (0.69 – 1.73)	0.700
	Nerve Injury	119 (31.6)	39 (44.8)	1.76 (1.09 – 2.82)	0.020
	Fracture	191 (45.5)	81 (90.0)	10.8 (5.3 – 22.1)	< 0.0001
Soft tissue injury	None / minimal	102 (32.2)	1 (1.2)	1.0	
	Moderate	186 (58.7)	19 (22.6)	2.65 (0.97 – 7.23)	0.058
	Severe	29 (9.1)	64 (76.2)	54.3 (20.1 – 147.0)	< 0.0001
Shock	None	231 (53.7)	27 (31.0)	1.0	
	Compensated	119 (27.7)	19 (21.8)	1.37 (0.73 – 2.56)	0.330
	Uncompensated	80 (18.6)	41 (47.1)	4.39 (2.53 – 7.59)	< 0.0001
Compartment syndrome		25 (5.7)	7 (7.1)	1.40 (0.59 – 3.34)	0.449
Ischaemic time	> 6 hours	1 (0.4)	10 (20.8)	28.8 (8.1 – 103.1)	< 0.0001
Arterial repair	Primary repair	75 (17.6)	11 (12.6)	1.0	
	Interposition graft	205 (48.1)	54 (62.1)	1.80 (0.89 – 3.62)	0.101
	Ligation	146 (34.3)	22 (25.3)	1.03 (0.47 – 2.23)	0.946

Data is presented as number (percent).

OR, Odds Ratio; CI, Confidence Interval; MOI, Mechanism Of Injury.

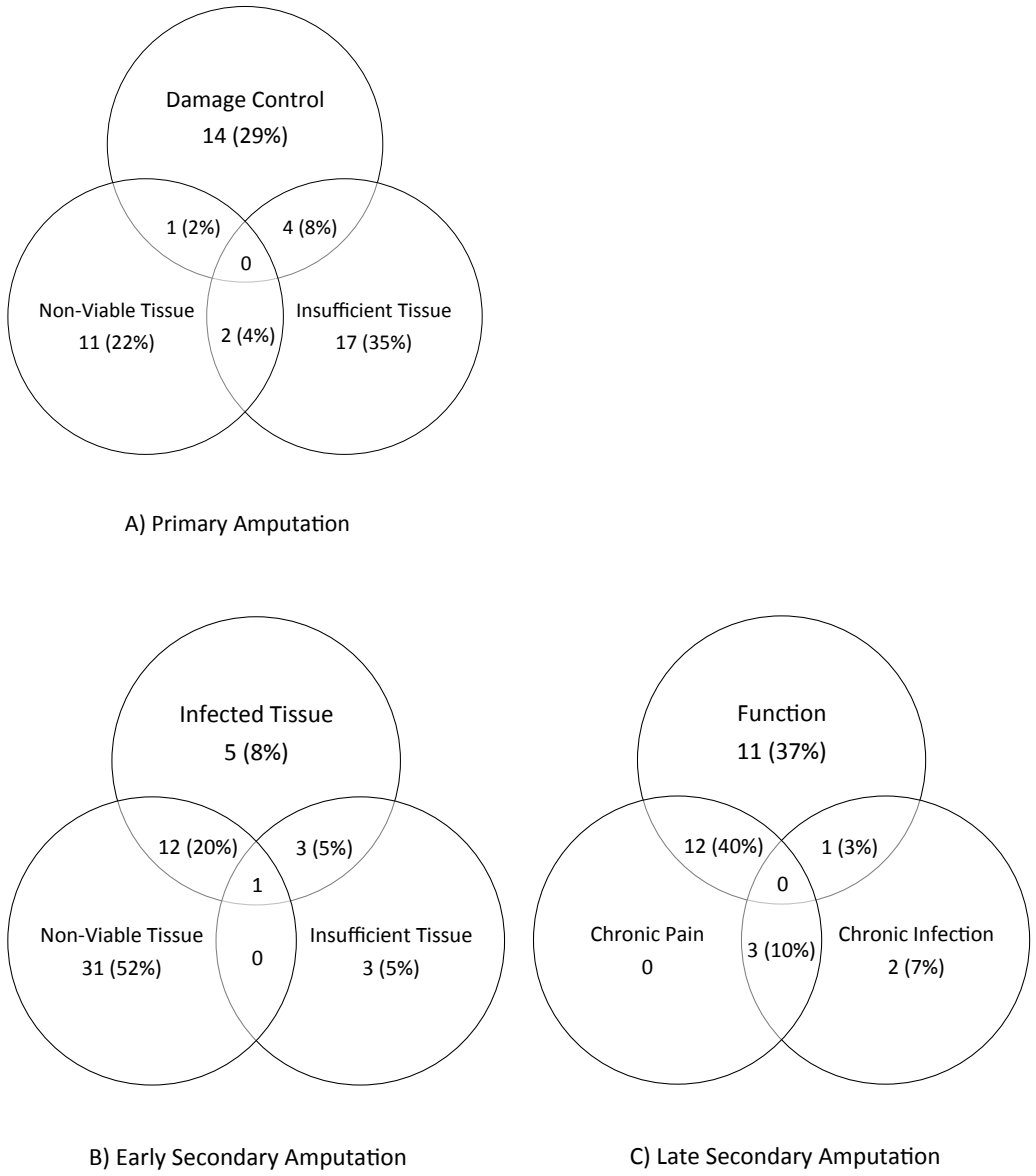


Figure 3.3: Venn diagrams demonstrating the key reasons for lower limb amputation in 579 soldiers with limb threatening injuries. A) 49 soldiers who underwent primary amputation, B) 60 soldiers who underwent early (≤ 30 days) secondary amputation, and C) 30 soldiers who underwent late (> 30 days) secondary amputation. Five soldiers in the early secondary amputation group and one soldier in the late secondary amputation group underwent amputation for reasons other than the three key reasons presented.

3.4.6 Level of Amputation

The most common level of amputation was trans-tibial (n=79, 56.8 percent), followed by trans-femoral (n=42, 30.2 percent), through-knee (n=9, 6.5 percent), and hip-disarticulation (n=9, 6.5 percent). Compared to primary amputations, a higher proportion of secondary amputations were performed at the trans-tibial level ($p = 0.210$), while hip-disarticulation was a significantly less common secondary procedure ($p = 0.009$) (Figure 3.4).

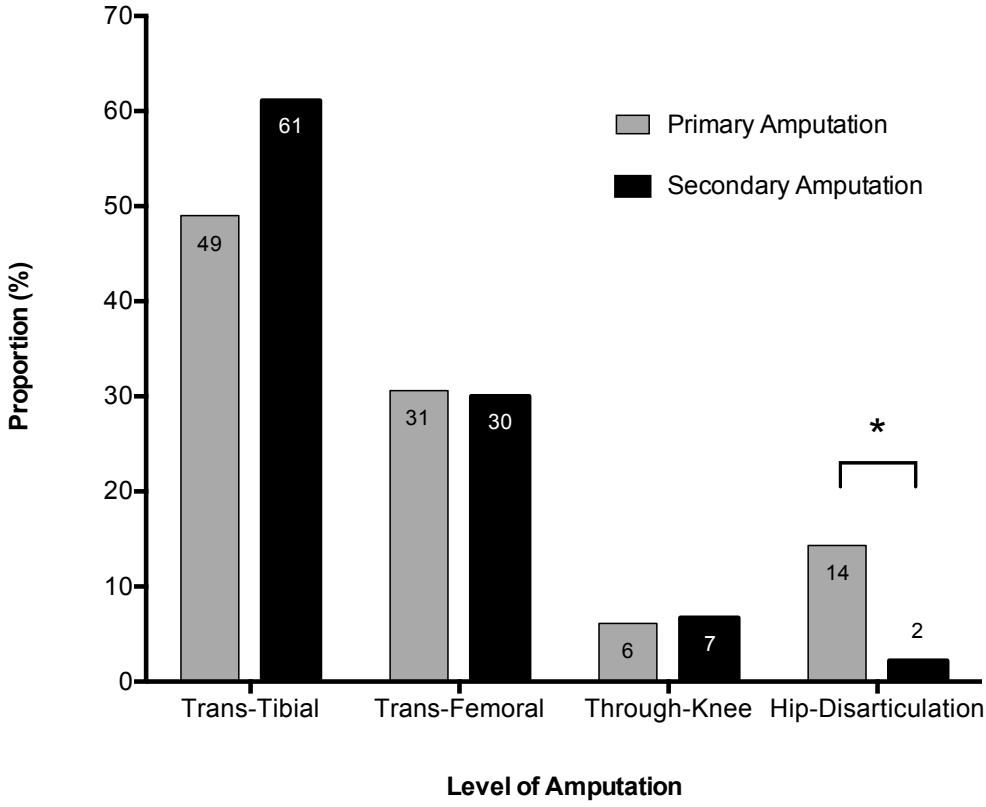


Figure 3.4: Anatomical level at which limb amputation was performed, according to the timing of the procedure. * Indicates a significant ($p < 0.05$) difference between groups.

3.5 Discussion

Key findings

While the majority of severe lower limb injuries sustained in battle are salvaged (Stansbury et al., 2008), nearly one quarter of those that involve a lower limb vascular injury may ultimately be treated with limb amputation. This study describes fundamental elements of clinical reasoning and surgical decision-making following these injuries, including the treatment decisions (what), the rationale for these decisions (why), the clinical characteristics associated with decisions (who), and the time-frames that decisions were made in (when).

Within hours of injury, approximately eight percent of injured limbs underwent primary amputation. A further seventeen percent of limbs underwent secondary amputation following an attempt at limb salvage. Two thirds of secondary amputations were performed early, within 30 days of injury, while a third were performed more than 30 days after injury (late). Approximately ten percent of lower limb amputations were performed more than one year after injury.

There were clear differences in the rationale for primary, early secondary, and late secondary amputations. Nearly half of primary amputations were performed because insufficient tissue remained for limb salvage. The remainder required amputation to facilitate resuscitation from uncontrolled haemorrhage or to remove non-viable tissue. This latter group of patients is important as they represent potentially avoidable amputations with advances in trauma systems and Damage Control Resuscitation.

The key reasons for early secondary amputation were non-viable limb tissue and sepsis, whilst the key reasons for late secondary amputations were functional limitation, chronic pain, and chronic infection.

Comparison to existing literature

The Lower Extremity Assessment Project (LEAP) studied a prospective cohort of 601 civilians with high-energy lower limb-threatening injuries, treated at eight US level-1 trauma centres (Bosse et al., 2002). The primary amputation rate was 11.3 percent and the secondary amputation rate after long-term follow-up was 17 percent (Bosse et al., 2001, MacKenzie et al., 2005). While this study was performed more than 15 years ago, it remains the best evidence to date informing the management of severe lower limb trauma and forms an important benchmark. A more recent analysis of the management of 1354 severe lower limb injuries across 222 US trauma centres, demonstrated a primary amputation rate of 9 percent and an early secondary amputation rate of 11 percent (de Mestral et al., 2013). This study did not report outcomes after hospital discharge, which may explain the low secondary amputation rate. Delayed amputations make up an important proportion of the overall amputation rate. In both the LEAP study and our study, the delayed amputation rate was approximately five percent.

Although not directly comparable, the primary amputation rate in our study is lower than the rate in these civilian studies, despite the more severe military injuries. This may reflect military advances in trauma care. The military have led developments in early haemorrhage control, haemostatic resuscitation, and limb reperfusion (Kragh et al., 2009, Holcomb et al., 2007a, Rasmussen et al., 2006b). Together, these interventions may make limb salvage attempts feasible in a greater proportion of casualties (Schreiber, 2012, Fox et al., 2010).

Despite the extensive medical literature on limb salvage versus amputation following trauma, the reasoning behind decision-making is rarely described (NICE, 2016). Two studies, both published more than 25 years ago, describe the rationale for amputation decisions in an adequate sample of injured patients (Pozo et al., 1990, Robertson, 1991). In a series of 35 secondary amputations following civilian trauma, Pozo et al. found that all early procedures (<30 days following injury) were performed to remove necrotic

tissue, whereas late amputations (≥ 30 days following injury) were performed for reasons including sepsis (79 percent), non-union (75 percent), and pain or poor function (18 percent). Similarly, in a series of 65 secondary amputations following civilian trauma, Robertson found the most common reasons for early amputation were tissue necrosis (67 percent) and sepsis (17 percent), while the most common reasons for late amputation were sepsis (51 percent) and poor function (29 percent). While tissue necrosis and sepsis remain the key reasons for early secondary amputation in our cohort, functional limitations and chronic pain have become the predominant reasons for late amputation.

Implications of findings

The difficulty in amputation/ salvage decisions following severe limb trauma are well recognised (Lange, 1989, Busse et al., 2007, Hansen Jr, 1989). However, approximately 70 percent of primary amputations in this study were performed because of non-viable or insufficient remaining limb tissue. These decisions do not necessarily represent complex decision-making, as there are no feasible alternatives to amputation. If there is any doubt, contemporary guidance is to preserve all viable tissue and delay amputation decisions until more information and expertise is available (Clasper, 2007, Nanchahal J, 2009).

By contrast, over one third of primary amputations were performed as damage control procedures to facilitate the resuscitation of shocked patients. The majority of these cases had both viable and sufficient limb tissue for salvage; but all had life-threatening haemorrhagic shock, with some experiencing a period of traumatic cardiac arrest. Primary limb amputation may be necessary as a life-saving intervention in these situations. However, not all such cases require immediate amputation and alternative strategies, that retain limb salvage potential, are sometimes possible (Fox et al., 2010, Schreiber, 2012, Gruen et al., 2012). Indeed, 80 percent of severely shocked casualties in this study had an initial attempt at limb salvage, and two thirds of these attempts were successful. These decisions typify the classic ‘life over limb’ maxim and are amongst the

most difficult a surgeon can face. The information available to estimate risks and inform clinical judgement is frequently uncertain or incomplete, and errors or delays in decision-making may have profound consequences including death or unnecessary amputation.

Central to immediate decision-making, in severely injured patients, is the state of their coagulation function (Roberts et al., 2015, Brohi et al., 2003, Kashuk et al., 2010). Patients that develop an acute coagulopathy are at substantially increased risk of exsanguination and death (Brohi et al., 2003, Brohi et al., 2007a, Frith et al., 2010). In these patients resuscitation must take precedence over all other treatment goals (Jansen et al., 2009, Duchesne et al., 2010b). However, coagulation function is usually unknown at the time of decision-making as routine coagulation tests are unable to identify coagulopathy in a useful time frame, and clinical estimation of coagulopathy is unreliable (Davenport et al., 2011, Brohi, 2011, Mitra et al., 2011). The ability to rapidly identify coagulopathic trauma patients is therefore a key objective of current trauma research, which has the potential to significantly influence trauma care and informed decision-making (Gruen et al., 2012, Stanworth et al., 2010).

There were clear temporal differences in the reasons for secondary amputation. Early amputation decisions were predominantly influenced by clinical course, while late decisions were influenced by patient preference. The majority of early secondary amputations were performed because of non-viable limb tissue. The principle causes were failed revascularisation and progression of tissue necrosis, and in many cases non-viable tissue also became a source of sepsis. By contrast, late amputations were most frequently due to functional limitations, with many patients also suffering from chronic pain. Together, tissue viability and limb function were decisive factors in more than 80 percent of amputation decisions. These risks are often unclear early in the patients' course, making timely decision-making difficult. A means to accurately estimate the risk of developing a non-viable or poorly functioning limb would support informed and shared

decision-making, allow earlier and better quality decisions, and reduced internal conflict about treatment decisions.

Limitations

This study has a number of limitations. The retrospective design predisposes to a risk of information bias; however, every effort was made to ensure complete and high quality data. Database information was corroborated with contemporaneous medical records and, in some cases, the patient. Furthermore, a team of specially trained GWOT-VII research nurses worked to assure data quality and accuracy.

Missing data is an important cause of information bias. Overall, there was minimal missing data in this cohort. However, three variables (nerve injury, degree of soft tissue injury, and ischaemic time) had more than ten percent missing data despite a complete search of the related medical records. The results of analyses of these variables should therefore be interpreted with caution. Very few patients had coagulation data and it was therefore not possible to analyse the relationship between coagulopathy and surgical decisions in this cohort. This does however affirm that surgical decisions are frequently made blind to coagulation state. There is also potential for selection bias because it was not possible to locate, contact, and gain consent from all eligible US servicemen.

The findings of this study relate to the decisions and management of predominantly young and healthy military servicemen with high-energy blast mechanisms of injury, treated in well-resourced US military trauma facilities. These findings may therefore not be generalizable to civilian populations and less resourced trauma systems. However, in many respects the findings do represent best-case scenario decision-making, with minimal influence from additional factors such as co-morbidities, cost, and resource limitations.

CHAPTER FOUR

Early Prediction of Trauma-Induced Coagulopathy

4.1 Introduction

4.1.1 Lower Limb Trauma Decision-Making During Resuscitation

Following severe lower limb trauma, initial therapeutic decisions centre on saving life, and to a large degree are based on intuitive predictions of the patients' physiological condition and their risk of death. Bleeding patients at risk of developing a coagulopathy are particularly important to identify, as this complication exacerbates haemorrhage and substantially increases the risk of preventable death (Brohi et al., 2003). Early activation of Damage Control protocols, to control haemorrhage and correct coagulopathy, improve survival in these patients (Holcomb et al., 2013, Rotondo et al., 1993, Cotton et al., 2008). These life-saving interventions take priority over limb salvage, and impact lower-extremity injury management. Early initiation of Damage Control Resuscitation in at risk patients may prevent an established coagulopathy and limit physiological disturbance (Gruen et al., 2012). This may enable definitive limb salvage surgery at the first operation, including complex limb salvage techniques (Holcomb et al., 2007a, Schreiber, 2012). However, Damage Control Surgery may be necessary in those that remain coagulopathic. These strategies may abbreviate or delay limb salvage attempts, potentially jeopardising limb outcome. In certain situations, life-saving haemorrhage control may necessitate primary resuscitative limb amputation. The key indication for a damage control approach is the development of coagulation abnormalities in a bleeding patient (Kashuk et al., 2010, Roberts et al., 2015). It is therefore important to be able to identify coagulopathic patients when making damage control decisions, to ensure the best possible outcomes.

4.1.2 Trauma Induced Coagulopathy

Trauma is a global public health problem and a leading source of the world's burden of disease (Lozano et al., 2012, Murray et al., 2012, Vos et al., 2012). A key complication

following trauma is the early development of clotting disorders (Brohi et al., 2003). Patients that develop a coagulopathy suffer substantially worse outcomes, with significantly higher rates of mortality, organ injury and infections (Brohi et al., 2003, Casstevens et al., 2010, Cohen et al., 2012). Furthermore, this patient group place a considerable demand on hospital resources with greater blood transfusion and ventilator requirements, and longer critical care and hospital length of stay (Brohi et al., 2007b, Maegele et al., 2007).

Effective therapeutic strategies, that target Trauma-Induced Coagulopathy (TIC), exist and the earlier these interventions are applied the greater the benefit (Roberts et al., 2011, Gruen et al., 2012, Duchesne et al., 2009, Sorensen and Fries, 2012, Rossaint et al., 2010). These damage control strategies focus on rapid haemorrhage control and early haemostatic resuscitation. They frequently involve abbreviated surgical procedures and the transfusion of large volumes of blood components. These strategies are life saving in patients at risk of coagulopathy, however, they may be harmful to patients if not indicated (Roberts et al., 2015).

Early identification of coagulopathic patients is needed for the effective initiation of these treatments (Kashuk et al., 2010). This enables rapid mobilisation of the required resources and allows targeted resuscitation of the patients most likely to benefit. Furthermore, in patients with normal coagulation, who derive no additional benefit from these therapies, the risks of unnecessary interventions and waste of precious resources may be minimised.

Although necessary, early identification of coagulopathic patients is not yet possible. Routine laboratory coagulation tests have limited accuracy in TIC, and results are not available in a useful timeframe to guide therapy (Davenport et al., 2011). Point-of-care prothrombin time assays are also imprecise in trauma (Davenport et al., 2011, Mitra et al.,

2012b). Thromboelastometry is better able to diagnose TIC and can provide results within a few minutes of collecting a blood sample (Davenport et al., 2011, Rugeri et al., 2007). However, although these complex devices are promising, they are not ideally suited to the emergency setting and are unlikely to be routinely available worldwide.

In the absence of a useful test, investigators have attempted to predict TIC (Mitra et al., 2011, Cosgriff et al., 1997). However, at the high sensitivities required to be clinically useful, these logistic regression models have poor specificity and are no better than clinical conjecture (Brohi, 2011). As a result, current practice relies on blind, unguided protocols, and the early identification of coagulopathic trauma patients remains a key research objective.

Advances in artificial intelligence provide the opportunity to develop accurate predictive models that can assist clinical decision-making. Bayesian Networks (BN's) are one example of these powerful technologies. BN's provide a framework for combining multiple sources of available information to compute the probability of an unknown outcome (Fenton and Neil, 2012b). They are particularly suited to situations were information may be missing or uncertain, as is often the case in the emergency setting.

4.2 Study Aims

The overall aim of this study was to develop a predictive model for the early identification of TIC in injured patients'.

The *first* objective was to develop a classification method for TIC that can serve as the reference standard to predict and test model performance against.

Second, to establish the clinical relevance of TIC in terms of resuscitation requirements and mortality.

Third, to systematically review the existing literature on causal mechanisms of TIC and construct an evidence-based causal network using the identified knowledge.

Finally, to develop a model that can accurately predict TIC from information that is normally available following an initial patient assessment.

4.3 Methods

4.3.1 Study design

The predictive model was developed using Bayesian Networks (BNs), a powerful technology that permits multiple sources of information to be used to calculate predictions (Fenton and Neil, 2012b). BNs consist of two parts: a network structure that graphically describes the models variables and their relations, and a set of parameters that captures the strength of the relationship between variables. The BN structure and parameters were developed using a novel method that combines information from published evidence, expert knowledge, and data from a prospective cohort study (Yet et al., 2014a).

4.3.2 Study population

The Activation of Coagulation & Inflammation in Trauma (ACIT) study is a multi-national, prospective cohort study designed to identify the mechanisms by which the body's coagulation pathways are activated immediately following injury. Adult patients (>15 years) presenting directly to participating Major Trauma Centres, who meet local criteria for trauma team activation, are included. Exclusion criteria include: arrival in the emergency department > 2 hours after injury; prehospital administration of > 2000ml intravenous fluid; and burns covering > 5% of body surface area. Patients are retrospectively excluded if they decline consent, take anticoagulation medication, have moderate or severe liver disease, or a bleeding diathesis. The study was reviewed and approved by the National Research Ethics Committee of participating countries and written informed consent was obtained for all participants.

The development cohort consisted of data from the first 600 consecutive patients enrolled in the London ACIT study (The Royal London Hospital, London, UK) between January 2007 and October 2011.

4.3.3 Data collection

For the purposes of this study, data was prospectively collected on patient demographics, mechanism of injury, injury characteristics, prehospital and admission vital signs, treatment administered, and outcome. Blood samples were collected immediately on hospital arrival and used for standard laboratory coagulation tests, rotational thromboelastometry (ROTEM), and blood gas analysis. Anatomical injuries were described and classified according to the Abbreviated Injury Scale (AIS) and Injury Severity Score (ISS) by certified coders (Gennarelli, 2008, Baker et al., 1974). All patients were followed-up daily until hospital discharge or death.

4.3.4 Definitions

Massive transfusion was defined as a requirement of ten or more units of Packed Red Blood Cells (PRBCs) in the first 24 hours (Malone et al., 2006). For the purposes of this study, DCS was defined as immediate resuscitative surgery aimed at controlling active haemorrhage and restoring normal physiology. DCS procedures included resuscitative thoracotomy, emergency laparotomy, extra-peritoneal pelvic packing, temporary vascular shunts, and primary (life-saving) amputations, but excluded emergency craniotomy, exploratory laparotomy in patients' with normal physiology, wound debridement, and definitive fracture fixation.

4.3.5 Outcome

The primary outcome was a clinically relevant coagulopathy on arrival at hospital.

We used a systematic approach to classify each patient's coagulation status into normal or abnormal because standard coagulation assays have significant limitations in TIC (Davenport et al., 2011). Our approach consisted of three steps. First, all patients were classified according to the clinically accepted laboratory definition of Acute Traumatic Coagulopathy (ATC), an admission Prothrombin Time ratio (PTr) > 1.2 (Frith et al., 2010). Second, all patients were independently clustered into normal and abnormal

coagulation status using an expectation-maximisation (EM) algorithm (Lauritzen, 1995). As standard laboratory coagulation tests have recognised limitations when used to diagnose ATC (Brohi, 2011, Davenport et al., 2011), this machine-learning step was used to identify potential diagnostic errors (Yet et al., 2014a). The algorithm clustered patients according to their expected coagulation state based on the their admission clinical profile, PTr, Activated Partial Thromboplastin Time ratio (APTTr) and thromboelastometry (ROTEM, Pentapharm GmbH, Munich, Germany). Cases where the laboratory and machine-learning methods agreed were assigned the corresponding coagulation state as their final classification. Cases where the two methods disagreed, or the PTr sample had haemolysed, underwent expert review to determine a final classification.

The third step was an expert review. The coagulation experts were Dr Ross Davenport (Ph.D.), Mr Imran Raza, Dr Simon Glasgow (Ph.D.), and Dr Sirat Khan (Ph.D.), each investigating aspects of bleeding and coagulation following trauma at a doctorate or post-doctorate level. Two of four trauma coagulopathy experts independently reviewed the admission clinical, laboratory, and thromboelastometry information of discrepant cases to determine an overall coagulation state. Disagreement was resolved by consensus with a third expert. Experts had no knowledge of the structure or predictors of the diagnostic model, or the EM algorithm result. Inter-reviewer agreement was evaluated with the kappa statistic and expert consistency was evaluated on a random sample of 20 patients with known coagulation status.

4.3.6 Clinical relevance of outcome

A fundamental determinant of the clinically value of a predictive model is the relevance of the outcome it is developed to predict. The relevance of the trauma coagulopathy classification was assessed for a range of important clinical outcomes. Firstly, mortality within 24 hours of injury, in-hospital mortality, and survival time were compared between injured patients classified as having normal coagulation and those classified as coagulopathic. Survival time was measured in hours, for the first 24 hours after injury,

and then days following injury. Next, blood transfusion requirements in the first 24 hours following injury, and damage control surgery requirements, were compared between the two groups. Finally, the critical care length of stay and hospital length of stay was compared. The relative risk for each outcome was calculated to compare the difference between injured patients classified as coagulopathic and those classified as normal. All patients were followed up until either hospital discharge or death.

4.3.7 Model development

The BN model was developed using a novel methodology that allows the combination of data and existing knowledge (Yet et al., 2014a). The methodology follows an iterative, step-wise approach that is described below:

Step 1) Causal structure

The BN structure was derived from existing knowledge. This was informed by a review of causal relationships between trauma and development of coagulopathy. Articles were identified by an electronic search of the MEDLINE and EMBASE databases using a combination of the terms "trauma" and "coagulopathy", and limited to English publications. Original studies that provided evidence of the causal mechanisms of TIC were reviewed. A revised structure of Bradford Hill's criteria for causation was used to identify relevant evidence (Hill, 1965, Howick et al., 2009). The reference lists of relevant articles were searched manually for additional relevant studies. The reviewed articles were used to 1) identify possible causal factors of traumatic coagulopathy and therefore the variables to include in the model, 2) define clinically relevant states for identified variables and 3) define the relationships between variables.

Step 2) Predictors

The model is designed to provide an early prediction, following an initial patient assessment, of the risk of traumatic coagulopathy. The initial assessment of an injured

patient is known as the primary survey and is described in the American College of Surgeons Advanced Trauma Life Support manual (2012). Potential predictors were therefore limited to information that would normally be available following a standard primary survey. Predictors were then selected based on evidence-based coherence with the causal structure of traumatic coagulopathy identified in *Step 1*. To minimise the risk of over-fitting, and in contrast to traditional methods of developing predictive models, data-driven methods of selecting predictors were not used. Furthermore, collinear predictors were retained as they may strengthen the network and provide users with flexibility when predictor information is missing or uncertain.

Step 3) Parameter learning and cross-validation

A set of parameters, that quantifies the relationship between a variable and those variables related to it, was defined for each node. These parameters are probability values assigned to each of the possible states of the variable that the node represents. The parameters of a given node are conditioned on the possible states of its parent nodes. For nodes without parents, the parameter is estimated from the prior probability of the respective state occurring in the population of interest.

The models parameters were learned form ACIT data. Probability values were calculated for each node in the network using the standard Expectation-Maximisation (EM) algorithm (Lauritzen, 1995). The EM algorithm is an established method of computing parameters from incomplete datasets (Dempster et al., 1977). However, missing data for the majority of predictor variables was less than one per cent.

Following parameter learning, the predictive performance of the model was tested on the development dataset using ten-fold cross validation (Kohavi, 1995). In this approach, the development cohort is randomly divided into ten equal size samples. Nine samples are used to train the model and the performance is then tested on the remaining sample. The process is repeated ten-fold, with each sample used once as test data. The results are then combined to calculate a performance estimate. Using this method, the model is trained

and internally validated on two statistically independent cohorts containing all of the development data.

Step 4) Expert review and model refinement

The inaccurate predictions of a predictive model offer valuable lessons for model refinement. Following cross-validation, cases with inaccurate predictions were identified and reviewed. Possible causes of inaccuracies were investigated to identify 1) potential opportunities to improve the models structure, 2) potential data errors and 3) limitations in the models scope. Where potential opportunities to improve the model were identified, the development process returned to step 1, with any changes supported by published evidence. Where potential data errors were identified, the original clinical or research sources were examined to verify data accuracy. Limitations to the scope of the model were documented and are presented in the discussion section.

4.3.8 Performance

The model's predictive performance was assessed using multiple measures of discrimination, calibration and accuracy. Accurate predictions can discriminate between patients at low risk and high risk of an outcome. Discrimination was measured using the Area Under the Receiver Operating Characteristic curve (AUROC), sensitivity, and specificity. As early identification of traumatic coagulopathy may have such an impact on subsequent outcome, it is important that a predictive model operates at a high sensitivity for the condition (Brohi, 2011). For this reason we assessed performance at a pre-specified sensitivity of 90 percent.

Calibration measures whether the predicted probability agrees with that observed. Calibration was evaluated using the Hosmer-Lemeshow test statistic (HL) (Hosmer and Lemesbow, 1980) and by visual assessment of the predicted and observed frequency of coagulopathy in 10 equal groups stratified by risk. A low HL p-value indicates poor calibration.

Accuracy combines features of discrimination and calibration to measure how close, on average, predicted outcomes are to actual outcomes. Accuracy was evaluated with the Brier Score (BS) and the Brier Skill Score (BSS) (Brier, 1950, Weigel et al., 2007). The BS has a value between 0 (perfect model) and 1 (worst possible model) and the BSS has a range from - ∞ to 1 where a negative value indicates a worse prediction than the average probability, and 1 indicates a perfect model.

4.3.9 Sensitivity analysis

The impact of individual predictors on the models probability calculations was assessed using one-way sensitivity analyses. The results were plotted on a tornado graph to allow visual comparisons of the relative impact of each predictor variable in the final model (Fenton and Neil, 2012b).

4.3.10 Statistical analysis

Normal-quartile plots were used to test for normality. Numerical data are reported as median with interquartile range (IQR) and categorical data as frequency (n) and percentage (%). The Mann–Whitney U test was used to compare numerical data and Fisher's Exact test was used to compare categorical data. Outcome comparisons between groups are reported as a Relative Risk (RR) with their corresponding 95 percent Confidence Intervals (CI). The time from injury to death between groups was compared with the log-rank (Mantel-Cox) test, and the results are presented as Kaplan-Meier curves. AUROC results are reported with their corresponding 95 percent confidence intervals (CI). Inter-reviewer agreement for expert outcome classification was evaluated with the kappa statistic. Statistical analyses were performed using GraphPad PRISM v6 (GraphPad Software Inc., San Diego, CA, USA) and R statistical software (version 2.15.2). Statistical significance was set as a two tailed p-value of < 0.05. The Bayesian Network model was developed with, and is powered by, AgenaRisk software (Agena, London, UK).

4.4 Results

4.4.1 Baseline characteristics

Data from 600 patients included in the ACIT study were used to develop the model. Their median age was 35 (range: 16 - 95) years, 486 (81.0 percent) were male, and 475 (79.2 percent) suffered a blunt mechanism of injury. Baseline characteristics of the development cohort are shown in Table 1. The median time from injury to hospital admission was 83 (63 – 103) minutes. With the exception of admission body temperature, missing data for clinical variables was minimal (Table 4.1).

4.4.2 Outcome classification

Five hundred twenty nine (88.2 percent) patients had normal coagulation and 71 (11.8 percent) patients developed a coagulopathy following injury. Baseline characteristics of patients who developed a coagulopathy were significantly different to those with normal coagulation (Table 4.1).

Classification of coagulation status was achieved by agreement between laboratory and EM methods in 565 (94.2 percent) patients and by expert review in the remaining 35 (5.8 percent) patients. The reasons for expert review were 1) no available PTr result due to haemolysis of the blood sample (10 cases, 1.7 percent) and 2) a discrepancy between the laboratory and EM classification (25 cases, 4.2 percent). Inter-reviewer agreement on the coagulation status of patients requiring expert review was excellent ($\kappa = 0.94$ [95 percent CI: 0.88 – 1.0]) and expert consistency in a random sample of 20 patients with known coagulation status was perfect.

Table 4.1: Baseline characteristics of the development population.

Characteristic	Missing Data (%)	Development cohort (N=600)	Normal coagulation (N=529)	Coagulopathy (N = 71)	P-value[b]
Age – years (range)	<1	35 (16 – 95)	35 (16 – 95)	38 (16 – 86)	0.354
Gender - male	0	486 (81.0)	434 (82.0)	52 (73.2)	0.079
Mechanism of Injury - Blunt	0	475 (79.2)	414 (78.3)	61 (85.9)	0.162
Pre-Hospital fluid (ml)	<1	0 (0 – 500)	0 (0 – 250)	850 (500 – 1500)	< 0.0001
Primary Survey:					
Respiratory Rate [a]	3	20 (16 – 24)	19 (16 – 24)	20 (11 – 28)	0.649
Heat Rate	0	95 (76 – 118)	93 (76 – 114)	122 (90 – 139)	< 0.0001
Systolic Blood Pressure	2	130 (107 – 148)	132 (115 – 150)	87 (60 – 111)	< 0.0001
Body Temperature (°C)	40	35.8 (35.1 – 36.5)	35.9 (35.1 – 36.5)	34.9 (33.7 – 35.6)	< 0.0001
Glasgow Coma Scale[a]	<1	15 (11 – 15)	15 (12 – 15)	10 (4 – 13)	< 0.0001
Suspected Haemothorax	<1	89 (14.9)	69 (13.0)	20 (28.2)	0.002
Suspected pelvic fracture	<1	58 (9.7)	37 (7.0)	21 (29.6)	< 0.0001
Suspected long bone fracture	<1	132 (22.2)	107 (20.2)	25 (35.2)	0.006
FAST - Positive	<1	49 (8.2)	33 (6.2)	16 (22.5)	< 0.0001
Baseline Blood Gas Analysis:					
pH	2	7.35 (7.30 – 7.40)	7.36 (7.32 – 7.41)	7.15 (6.99 – 7.27)	< 0.0001
Lactate	5	2.1 (1.3 – 3.6)	2.0 (1.2 – 3.1)	6.2 (3.2 – 10.8)	< 0.0001
Base Deficit	2	1.8 (-0.2 – 4.4)	1.4 (-0.5 – 3.4)	10.8 (5.4 – 18.7)	< 0.0001
Baseline Thromboelastometry:					
EXTEM CA5 (mm)	3	44 (38 – 49)	45 (40 – 49)	28 (20 – 35)	< 0.0001
EXTEM MCF (mm)	3	61 (56 – 65)	61 (57 – 65)	49 (40 – 54)	< 0.0001
FIBTEM MCF (mm)	3	14 (10 – 17)	14 (11 – 18)	7 (5 – 9)	< 0.0001
Baseline laboratory values:					
INR	2	1.1 (1.0 – 1.1)	1.1 (1.0 – 1.1)	1.3 (1.3 – 1.6)	< 0.0001
APTT (seconds)	3	23 (22 – 26)	23 (22 – 25)	39 (29 – 61)	< 0.0001
Haemoglobin (g/dL)	5	13.9 (12.4 – 14.9)	14.1 (12.8 – 14.9)	11.4 (9.0 – 12.9)	< 0.0001
Platelet count ($x10^9$ /L)	5	231 (193 – 272)	234 (200 – 277)	173 (130 – 242)	< 0.0001
Injury severity:					
Injury Severity Score	0	16 (9 – 29)	13 (5 – 25)	34 (25 – 43)	< 0.0001
Head AIS ≥ 3	0	173 (28.8)	132 (25.0)	41 (57.8)	< 0.0001
Chest AIS ≥ 3	0	257 (42.8)	199 (37.6)	58 (81.7)	< 0.0001
Abdomen AIS ≥ 3	0	62 (10.3)	45 (8.5)	17 (23.9)	0.0003
Extremity AIS ≥ 3	0	198 (33.0)	156 (29.5)	42 (59.2)	< 0.0001

Data presented as number (%) or median (IQR) unless otherwise stated. [a] Admission measurement or, if patient arrived intubated, pre-hospital measurement prior to sedation and intubation. [b] P-value refers to difference between normal coagulation and coagulopathy groups. FAST, Focused Assessment with Sonography for Trauma; CA5, Clot Amplitude at 5 minutes; MCF, Maximum Clot Firmness; INR, International Normalised Ratio; APTT, Activated Partial Thromboplastin Time; AIS, Abbreviated Injury Score.

4.4.3 Clinical relevance of coagulopathy

Mortality

The mortality rate in the first 24-hours following injury was 36.6 percent in patients that developed a coagulopathy compared to 1.3 percent in patients with normal coagulation (RR: 27.7 (12.5 – 61.4); P < 0.0001). Similarly, in-hospital mortality was also substantially higher in coagulopathic patients compared to those with normal coagulation (53.7 percent versus 5.6 percent; RR: 10.2 (6.8 – 15.2); P < 0.0001) (Table 4.2). Injured patients that developed a coagulopathy were significantly less likely to survive their injuries than those with normal coagulation and the majority of deaths in coagulopathic patients occurred soon after injury (Figure 4.1).

Consumption of health care resources

In the first 24-hours after injury, coagulopathic patients more frequently required a blood transfusion (90.1 percent versus 23.2 percent; RR: 3.9 (3.3 – 4.6); P < 0.0001) and a massive transfusion (40.9 percent versus 1.3 percent; RR: 30.6 (13.9 – 67.3) P < 0.0001) when compared to non-coagulopathic patients (Table 4.2). On average, each coagulopathic patient was transfused 8 (5 – 15) PRBC units and 6 (3 – 9) Fresh Frozen Plasma (FFP) units, compared to a median of 0 (0 – 0) units of either in non-coagulopathic patients (p < 0.0001). Coagulopathic patients were also more likely to require immediate DCS than non-coagulopathic patients (45.1 percent versus 4.0 percent; RR: 11.4 (6.9 – 18.6); P < 0.0001). Additionally, coagulopathic patients that survived had significantly longer critical care (8 (4 – 16) days versus 0 (0-2) days; p < 0.0001)) and hospital (33 (20 – 47) days versus 8 (2 – 21) days; p < 0.0001) length of stay, compared to survivors with normal coagulation.

Table 4.2: Comparison of outcomes and resuscitation resource requirements in 600 injured patients stratified by coagulation status.

Outcome	Missing Data (%)	Coagulopathy (N=71)	Normal Coagulation (N=529)	Relative Risk (95% CI)	P-value
Mortality:					
24-hour	0	26 (36.6)	7 (1.3)	27.7 (12.5 – 61.4)	< 0.0001
Hospital	0	41 (57.8)	30 (5.7)	10.2 (6.8 – 15.2)	< 0.0001
Emergency intervention in first 24 hours:					
Transfusion	<1	64 (90.1)	122 (23.2)	3.9 (3.3 – 4.6)	< 0.0001
Massive transfusion	<1	29 (40.9)	7 (1.3)	30.6 (13.9 – 67.3)	< 0.0001
DCS	0	32 (45.1)	21 (4.0)	11.4 (6.9 – 18.6)	< 0.0001

Data presented as number (%)
Risk Ratios are for the coagulopathic group, as compared with the normal coagulation group.
DCS, Damage Control Surgery

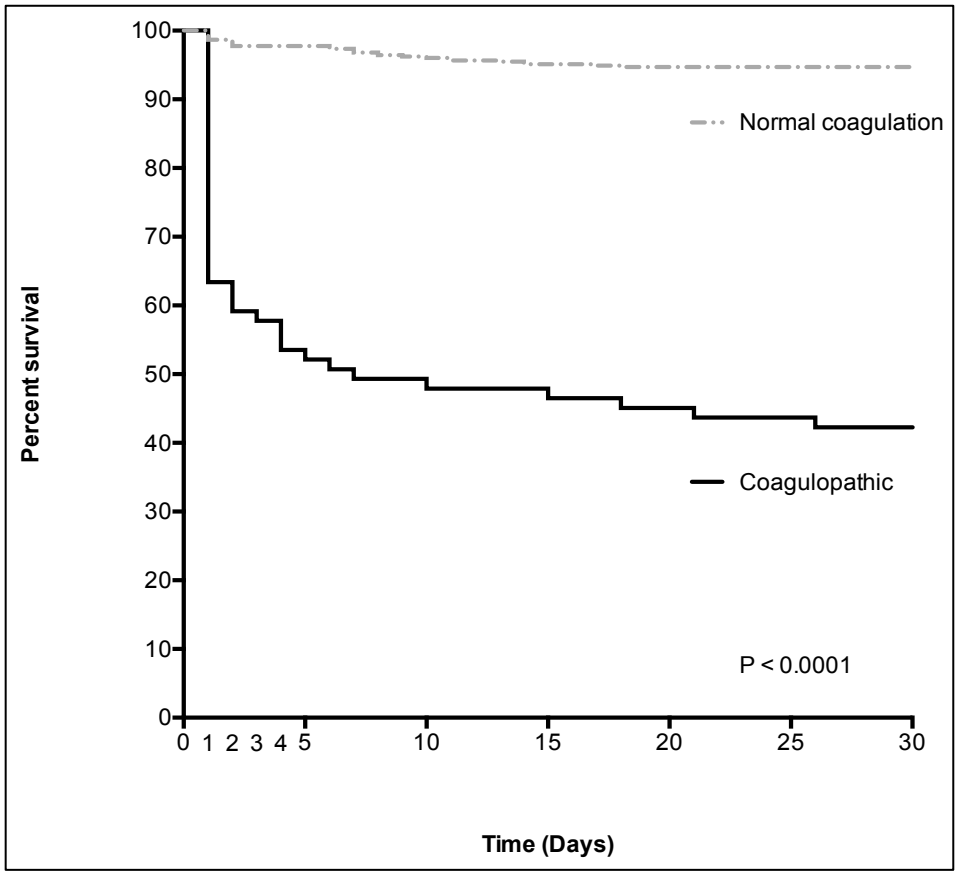


Figure 4.1: Kaplan-Meier estimates of the probability of survival for 600 injured patients with either normal coagulation or a coagulopathy. The P-value was calculated using the log-rank (Mantel-Cox) test.

4.4.4 Model development

Literature search

The literature search identified 1421 citations. These were screened and 262 potentially relevant full-text articles were reviewed. A further eleven articles were identified from the reference lists of reviewed articles. Eighty-five articles were excluded because of an ineligible study type: narrative review (78), letter or editorial (5), survey or guideline (2). Forty-one original articles were excluded as they only described the diagnosis (10) or treatment (22) of coagulopathy, or had no description of the causal mechanisms of traumatic coagulopathy (9). Overall, 147 original studies were included (Figure 4.2). These consisted of 87 observational studies (51 retrospective and 36 prospective), 58 experimental studies (35 Animal, 20 human, and 3 computer simulation), and two systematic reviews.

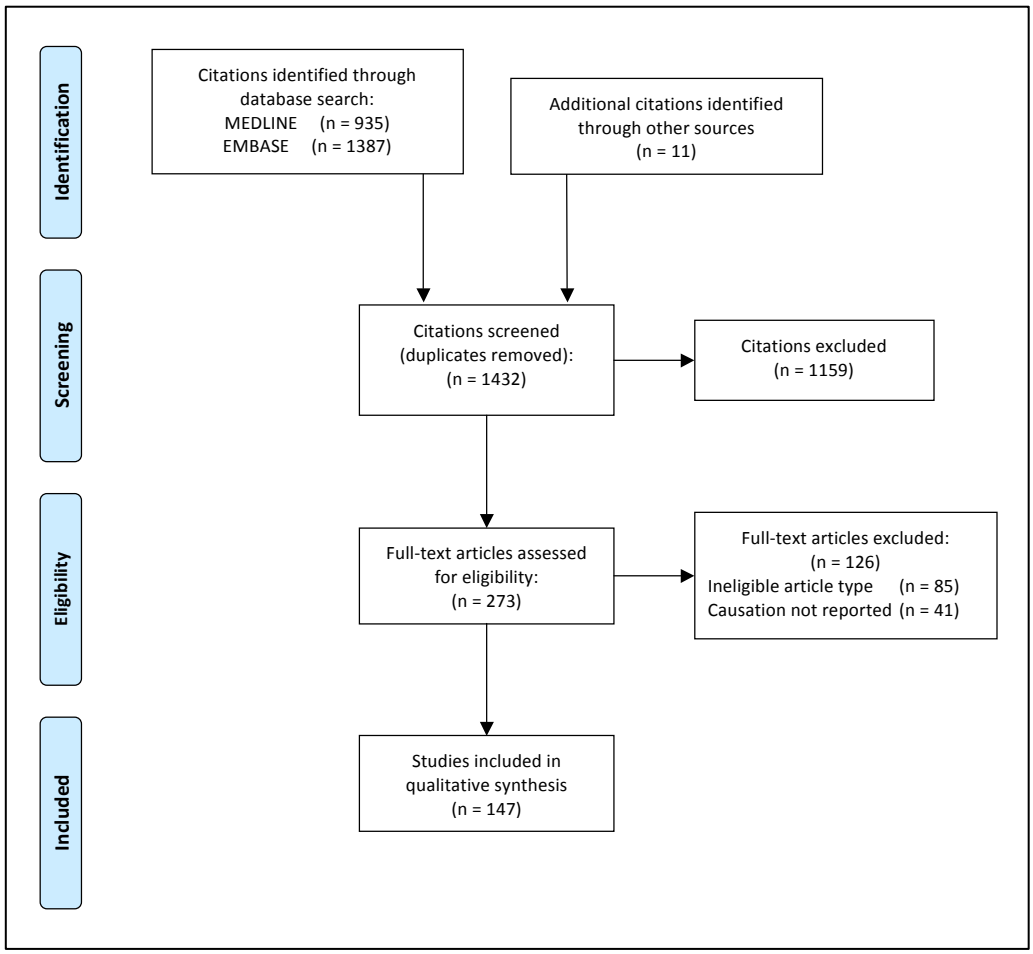


Figure 4.2: PRISMA flow chart of study selection process.

Causal structure

Evidence from the included studies was used to inform the causal structure of the Bayesian Network. The review identified several possible causes of traumatic coagulopathy that are frequently interrelated. These causes are related to characteristics of the injury, degree of physiological derangement, and subsequent medical intervention. Some causal factors (tissue injury and tissue hypoperfusion) may immediately effect coagulation, while others (acidaemia, hypothermia, haemodilution) may take time to develop and therefore take time to exert their effect. Evidence supporting the identified causal factors is presented in Table 4.3 and qualitatively described below. These causal factors formed the core structure of the prognostic model. (Fig 4.3)

Hypoperfusion

Systemic tissue hypoperfusion following trauma appears to be a principal cause of an early endogenous coagulopathy. The predominant cause of tissue hypoperfusion after trauma is haemorrhagic shock but tension pneumothorax, cardiac tamponade and central nervous system injury may occasionally contribute (ACS, 2012). Observational studies of heterogeneous trauma populations, from a wide spectrum of geographic and socioeconomic settings, repeatedly demonstrate a strong correlation between systemic markers of tissue hypoperfusion and acute coagulation dysfunction. These markers include heart rate (Cohen et al., 2013), systolic blood pressure (Cohen et al., 2013, Cosgriff et al., 1997, Cotton et al., 2011, Kashuk, 2012, Mitra et al., 2011, Raza et al., 2013, Talving et al., 2009, Wafaisade et al., 2010), lactate (Kashuk, 2012) , and base deficit (Brohi et al., 2007b, Brohi et al., 2008, Brophy et al., 2013, Cap and Spinella, 2011, Casstevens et al., 2010, Cheddie et al., 2013, Cohen et al., 2007, Cohen et al., 2012, Cohen et al., 2013, Cotton et al., 2011, Davis et al., 1996, Frith et al., 2010, Kapsch et al., 1984, Kashuk, 2012, Nardai et al., 2009, Simmons et al., 2011, Sixta et al., 2012, Wafaisade et al., 2010, Xu et al., 2013, Raza et al., 2013). Furthermore, experimental animal models that combine trauma and haemorrhagic shock are able to consistently

induce an endogenous acute traumatic coagulopathy (Burruss et al., 2012, Chesebro et al., 2009, Darlington et al., 2012a, Frith et al., 2012, Frith et al., 2010, Harr et al., 2011, Letson et al., 2012, Martini et al., 2005a, Park et al., 2013, White et al., 2010b, Darlington et al., 2013, White et al., 2010a). Many of these models carefully control for known exogenous confounders including hypothermia and haemodilution (Chesebro et al., 2009, Darlington et al., 2012a, Darlington et al., 2013, Frith et al., 2012, Frith et al., 2010, White et al., 2010a). In addition, endogenous coagulopathy only appears to occur in the presence of tissue hypoperfusion (Brohi et al., 2007b, Brohi et al., 2008, Cohen et al., 2007, Frith et al., 2011) and there is a clear dose-response relationship between the degree of tissue hypoperfusion and coagulation dysfunction (Brohi et al., 2007b, Davis et al., 1996, Frith et al., 2010, Jansen et al., 2011, Kapsch et al., 1984, Raza et al., 2013). Although tissue hypoperfusion alone can cause coagulation dysfunction, this seems to be greatly amplified when combined with some degree of tissue injury (Frith et al., 2010). Tissue hypoperfusion appears to cause coagulopathy by activation of anticoagulant and fibrinolytic pathways (Brohi et al., 2007b, Brohi et al., 2008, Cohen et al., 2012, Jansen et al., 2011, Kashuk, 2012, Martini et al., 2005a, Raza et al., 2013). These mechanisms appear to be mediated through the effects of thrombomodulin on thrombin, activation of protein C and endothelial release of tissue plasminogen activator (Brohi et al., 2007b, Brohi et al., 2008, Kashuk, 2012, Raza et al., 2013, Cohen et al., 2012, Hrafnkelsdottir et al., 2001). In parallel, coagulopathy is also commonly observed following other causes of systemic hypoperfusion such as severe sepsis (Walsh et al., 2010), severe burns (Sherren et al., 2013) and cardiac arrest (Lee et al., 2012, White et al., 2011b, Adrie et al., 2005). The similarity of these findings strongly supports a causal hypothesis between systemic tissue hypoperfusion and coagulopathy.

Tissue Injury

Tissue injury activates normal coagulation pathways by exposing tissue factor to blood (Banner et al., 1996, Hoffman and Monroe, 2001). By definition, all trauma patients have

some degree of tissue injury. The extent depends on the mechanism of injury, the amount of energy transferred, and the proportion of the body involved. As no validated biomarker exists, the extent of tissue injury is commonly estimated using the Injury Severity Score (ISS). The ISS is an anatomical score that measures the overall severity of injured patients (Baker et al., 1974). Each distinct injury in an individual patient is assigned an Abbreviated Injury Scale (AIS) score (Gennarelli, 2008). AIS scores range from 1 (minor) to 6 (lethal) and are defined in an internationally recognised dictionary. The ISS then divides the body into six regions (head, face, chest, abdomen, extremities including pelvis, and external) and the score is calculated by adding the square of the highest AIS score in the three most severely injured body regions.

There is a significant association between coagulopathy and the extent of tissue injury, as measured by ISS (Affonseca et al., 2007, Brohi et al., 2003, Brophy et al., 2013, Cheddie et al., 2013, Cohen et al., 2012, Cosgriff et al., 1997, Cotton et al., 2011, Floccard et al., 2012, Frith et al., 2010, Genet et al., 2013, Johansson et al., 2011, Kapsch et al., 1984, Nardai et al., 2009, Niles et al., 2008, Raza et al., 2013, Shaz et al., 2011, Simmons et al., 2011, Sixta et al., 2012, Wafaisade et al., 2010, Xu et al., 2013). Furthermore, there appears to be a dose-response relationship between ISS and the proportion of patients that develop a coagulopathy (Brohi et al., 2003, Floccard et al., 2012, Kapsch et al., 1984, Lustenberger et al., 2010). The components of the ISS that appear to contribute to this relationship are increasingly severe injuries to the head, chest, abdomen, and extremity AIS body regions, but not isolated face and external injuries (Brohi et al., 2003, Talving et al., 2009, Wafaisade et al., 2010). Coagulation dysfunction appears to only develop, however, when tissue injury is combined with tissue hypoperfusion (Brohi et al., 2007b, Cohen et al., 2007). Animal models confirm this observation: animals subjected to a combination of tissue injury and tissue hypoperfusion predictably develop an early coagulopathy, while coagulation remains normal in animals subjected to tissue injury alone (Frith et al., 2010). Although ISS is designed to reflect the extent of tissue injury, it

may also act as a marker of the volume of blood loss and shock. This is a potentially important confounder when using ISS as a measure of tissue injury.

A number of specific injuries are associated with an increased risk of coagulopathy. Traumatic Brain Injury is strongly associated with coagulopathy (Cap and Spinella, 2011, Chhabra et al., 2013, Lustenberger et al., 2010, Zehtabchi et al., 2008, Carrick et al., 2005, Greuters et al., 2011, Harhangi et al., 2008). The severity of the brain injury, as measured with the Glasgow Coma Scale or head AIS score, directly correlates with the risk of developing coagulopathy (Affonseca et al., 2007, Cap and Spinella, 2011, Chhabra et al., 2013, Cohen et al., 2013, Talving et al., 2009, Xu et al., 2013, Keller et al., 2001, Lozance et al., 1998, Peiniger et al., 2012, Brohi et al., 2003, Lustenberger et al., 2010). Major pelvic fractures (Cordts et al., 2011, Filho et al., 2011, Poole et al., 1992) and severe intra-abdominal haemorrhage (Rotondo et al., 1993, Garrison et al., 1996) are also associated with a high risk of developing coagulopathy. Indeed, even clinically suspected pelvic fractures or intra-abdominal injuries are predictive of coagulopathy (Mitra et al., 2011). These injuries may be markers of overall tissue injury severity, risk factors for haemorrhage and shock, or instigators of specific causal mechanisms. Thus, tissue injury appears to be an important initiator of coagulation and fibrinolysis, but alone, does not appear to cause coagulation dysfunction.

Acidaemia

Acidaemia is defined as a blood pH less than 7.35 - the lower limit of normal. Following injury, acidaemia is usually caused by a lactic acidosis resulting from shock and tissue hypoperfusion. Other potential causes of acidaemia in trauma patients include excess chloride administration, respiratory failure, and a lactic acidosis due to intense physical exertion.

A strong association between acidaemia and coagulopathy is observed in injured patients (Cosgriff et al., 1997, Engels et al., 2011, Ferrara et al., 1990, Kashuk, 2012, Aucar et al.,

2003). Furthermore, severe acidaemia (pH 7.1), induced by controlled haemorrhage and tissue hypoperfusion, causes a coagulopathy in animal models (Darlington et al., 2011, Dubick et al., 2009). It is difficult, however, to separate the effects of acidaemia and those of tissue hypoperfusion on coagulation function. Experimentally inducing acidaemia, using exogenous acid, impairs coagulation in both animal models (Darlington et al., 2011, Frith et al., 2012, Martini et al., 2006, Martini et al., 2005b) and human blood (Engstrom et al., 2006). These derangements seem to be the result of impaired coagulation protease and platelet function (Dubick et al., 2009, Martini et al., 2006, Martini et al., 2007, Martini et al., 2005b). Worsening acidaemia has a dose-dependant effect on clotting function (Engstrom et al., 2006, Kashuk, 2012). However, reversal of the acidaemia does not appear to correct the coagulopathy (Martini et al., 2007, Martini et al., 2006, Darlington et al., 2011, Dubick et al., 2009).

Hypothermia

Hypothermia is defined as a core body temperature of less than 35°C (ACS, 2012). Following injury, hypothermia may be caused by 1) an increase in heat loss resulting from environmental exposure, infusion of cold fluids, or the administration of anaesthetic drugs; and/or 2) a decrease in heat production due to tissue hypoperfusion and reduced metabolism in shocked patients.

Observational studies have identified a significant association between hypothermia and coagulopathy in trauma patients (Cohen et al., 2013, Cosgriff et al., 1997, Ferrara et al., 1990, Ferraro et al., 1992, Ireland et al., 2011, Mitra et al., 2011, Wafaisade et al., 2010, Xu et al., 2013). Hypothermia inhibits coagulation proteases and platelet function (Watts et al., 1998, Wolberg et al., 2004, Kermode et al., 1999, Martini et al., 2005b) in a dose-dependant and reversible manner (Kashuk, 2012, Mitrophanov et al., 2013, Shcherbina et al., 2013, Michelson et al., 1994). These changes prolong clotting times but do not seem to affect the strength of formed clots (Darlington et al., 2012b, Martini et al., 2008, Park et al., 2013). However, clinically significant effects on coagulation function are only

observed at temperatures below 33°C (Wolberg et al., 2004, Martini et al., 2005b, Meng et al., 2003). Above this temperature, mildly hypothermic trauma patients have similar coagulation function to normothermic patients (Brohi et al., 2008, Mohr et al., 2013, Watts et al., 1998). Temperatures below 33°C are uncommon in trauma patients (Martin et al., 2005, Wang et al., 2005), suggesting that alternative causes of coagulopathy are also involved in injured patients.

Dilution

In hypovolaemic shock, intracellular and extracellular fluid shifts into the plasma resulting in dilution of the blood constituents. This haemodilution is greatly compounded by resuscitation with intravenous fluids. Early trauma coagulopathy is associated with haemodilution as measured by admission haemoglobin concentration (Kashuk, 2012), haematocrit (Shaz et al., 2011), and the volume of pre-hospital fluid administered (Cohen et al., 2013, Hubetamann et al., 2011, Maegele et al., 2007, Rourke et al., 2011, Shaz et al., 2011, Sixta et al., 2012, Wafaisade et al., 2010). Furthermore, the degree of coagulation dysfunction correlates with the degree of haemodilution and the volume of pre-hospital fluid administered in a dose-dependant manner (Darlington et al., 2010, Maegele et al., 2007, Kashuk, 2012). The degree of shock and haemodilution, however, are closely correlated and it is again difficult to separate the clinical effects of tissue hypoperfusion from those of haemodilution on coagulation function. The independent coagulopathic effects of haemodilution have been demonstrated in experimental animal models (Dickneite et al., 2010, Dickneite and Pragst, 2009, Frith et al., 2012, Grottke et al., 2010), computer simulation models (Hirshberg et al., 2003, Ho et al., 2009), in-vitro human blood (Darlington et al., 2010, Darlington et al., 2012b, Bolliger et al., 2010, Ogweno and Gwer, 2013, Brazil and Coats, 2000), and in healthy human volunteers (Coats et al., 2006). As expected, administration of large volumes of intravenous fluid has a clear dilution effect on platelets and coagulation proteases, which results in a decrease in thrombin generation, prolonged clot formation, and reduced clot strength (Dickneite et

al., 2010, Dickneite and Pragst, 2009, Frith et al., 2012, Ogweno and Gwer, 2013). Furthermore, crystalloid dilution may increase fibrinolysis and colloids may directly interfere with clotting function (Bolliger et al., 2010, Brummel-Ziedins et al., 2006, Coats et al., 2006). The effects of haemodilution may be minimised or reversed by volume resuscitation with blood products in ratios that replicate whole blood (Hirshberg et al., 2003, Ho et al., 2009). Haemostatic resuscitation principles aim to minimise haemodilution and its negative effects, however, significant early coagulopathy frequently occurs in patients with no haemodilution and who receive minimal resuscitation fluid, suggesting alternative causes may be more important in early coagulopathy (Brohi et al., 2003).

Table 4.3: Evidence supporting the identified causal factors presented according to a revised framework of the Bradford Hill criteria (Howick et al., 2009).

Causal evidence	Tissue Hypoperfusion	Tissue Injury	Acidaemia	Hypothermia	Haemodilution
Direct evidence					
Association	🟢	🟢	🟢	🟢	🟢
No confounding[a]	🟢	🔴	🟢	🟢	🟢
Temporality	🟢	🟢	🟢	🟢	🟢
Dose-responsiveness	🟢	🟢	🟢	🟢	🟢
Reversibility	🟠	🔴	🔴	🟢	🟢
Mechanistic evidence					
Plausible mechanism	🟢	🟢	🟢	🟢	🟢
Parallel evidence					
Replicability	🟢	🟢	🟢	🟢	🟢
Similarity	🟢	🔴	🟢	🟢	🟢

[a] Have plausible confounders been adjusted for?

🟢 Supporting evidence, 🟠 unclear evidence, 🔴 no supporting evidence

Predictors

The literature search identified a number of potential predictors that would normally be available following a standard primary survey. Additional predictors were identified from the Advanced Trauma Life Support (ATLS) primary survey guidelines (ACS, 2012). The estimated energy and mechanism of injury provide valuable information that can be used to identify patients with severe injuries and at high risk of severe haemorrhage (Spahn et al., 2013, Schreiber et al., 2007, Sasser et al., 2012). Furthermore, the primary survey prioritises the identification of certain "life-threatening" injuries because of their association with significant haemorrhage and shock. These include injuries that result in haemothorax, cardiac tamponade, and intra-abdominal bleeding, as well as major pelvic and long bone fractures. Aside from clinical examination, X-ray of the chest and pelvis in conjunction with ultrasonography are recommended diagnostic modalities during the primary survey to assist with the identification of these injuries.

Fourteen predictor variables were incorporated in the final model (Table 4.4). The relationships between predictor variables, causal variables and outcome are captured by the network structure of the final model (Fig 4.3). Full details of the literature search results and the evidence supporting the final models structure are presented in an evidence browser (Yet et al., 2014b). The browser is available at http://www.traumamodels.com/atcbn/ATC_EBase/index.html.

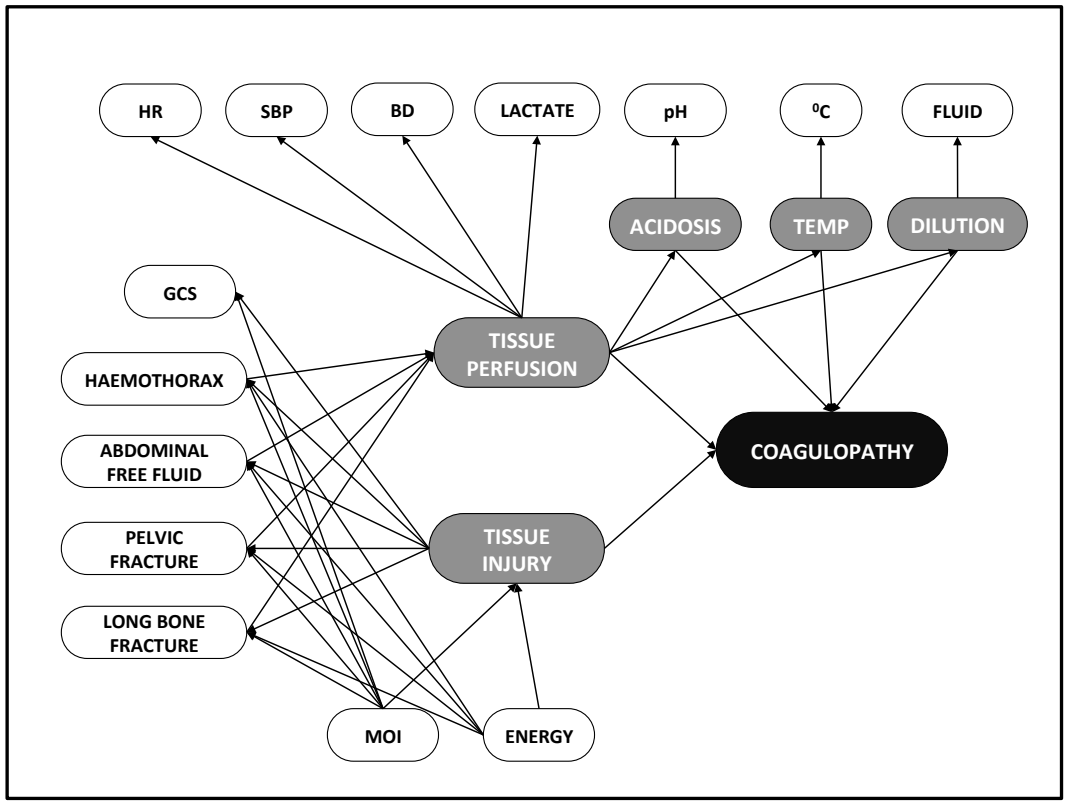


Figure 4.3: Structure of the Bayesian Network predictive model. The black variable represents the primary predicted outcome. Grey variables represent the five identified causal factors, and white variables represent identified predictors associated with the causal factors. HR, Heart Rate; SBP, Systolic Blood Pressure; BD, Base Deficit; °C, measured temperature in degrees Celsius; Fluid, volume of prehospital resuscitation fluid administered; GCS, Glasgow Coma Scale; MOI, Mechanism Of Injury; Temp, Temperature.

Table 4.4: Definitions of predictor variables in the Bayesian Network model.

Predictor Variable	Type of Node	Definition
Heart rate	Continuous	Heart rate in beats per minute
Systolic blood pressure	Continuous	Systolic Blood Pressure in mmHg
Temperature	Boolean	≥ 34 °C / < 34 °C
Haemothorax	Boolean	*Present*: Clinically suspected, based on examination or CXR findings. *Absent*: Not suspected
FAST result	Boolean	*Positive*: Free peritoneal fluid identified. *Negative*: No free peritoneal fluid or investigation not clinically indicated.
Unstable pelvic fracture	Boolean	*Present*: Clinically suspected, based on examination or PXR findings. *Absent*: Not suspected
Long bone fracture	Boolean	*Present*: Clinically suspected fracture of femur, tibia or humerus. Traumatic amputation proximal to ankle or elbow. *Absent*: Not suspected
GCS	Ranked	Glasgow Coma Score on admission or prior to intubation
Lactate	Continuous	Admission Arterial or Venous Blood Gas Analysis
Base Deficit	Continuous	Admission Arterial or Venous Blood Gas Analysis
pH	Continuous	Admission Arterial or Venous Blood Gas Analysis
Mechanism of Injury	Boolean	*Blunt / Penetrating*
Energy	Boolean	*High-Energy*: High-velocity GSW; fall > 20 feet (6 meters); Pedestrian or cyclist versus vehicle > 20mph; Road Traffic Collision with mechanical entrapment, ejection from vehicle or death in same passenger compartment; Entrapment under a train or vehicle; Crush injury; Blast injury. *Low-Energy*: Stab; low-velocity GSW; and blunt injury excluding injuries above.
Volume of fluid administered	Ranked	1) < 500ml, 2) 500 – 2000ml, 3) > 2000ml crystalloid or colloid fluid.

CXR, Chest X-Ray; PXR, Pelvic X-Ray; GSW, Gun Shot Wound

4.4.5 Performance

The model had excellent overall performance at predicting traumatic coagulopathy in the development cohort. The AUROC was 0.927 (95 percent CI: 0.902 – 0.953) and at a sensitivity set at 90 percent, the specificity was 82 percent (Figure 4.4). The predicted risk of coagulopathy calibrated well with observed risk (Figure 4.5) and the Hosmer-Lemeshow goodness-of-fit test result was non-significant (P = 0.3). Furthermore, the models predictions were accurate, with a Brier Score of 0.06 (95 percent CI: 0.05 – 0.08) and a Brier Skill Score of 0.39 (95 percent CI: 0.28 – 0.50).

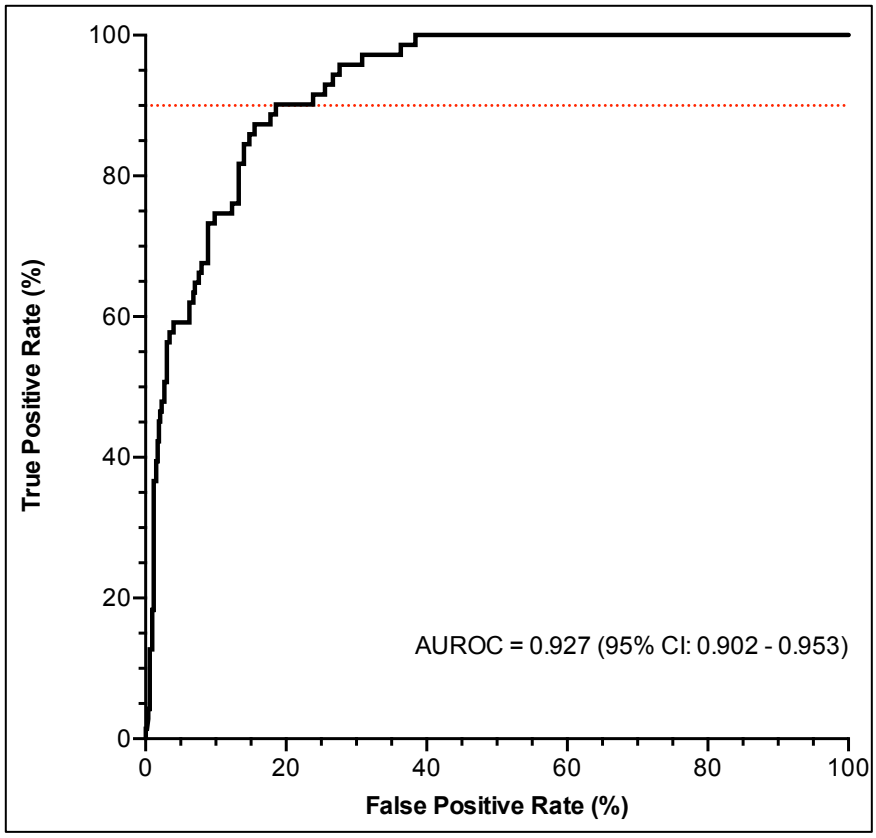


Figure 4.4: Overall accuracy of the trauma-induced coagulopathy predictive model. Overall accuracy was assessed using the Receiver Operating Characteristic (ROC) curve for coagulopathy predictions in the development cohort. This plots the true positive rate (sensitivity) against the false positive rate (1 – specificity). The Area under the ROC curve (AUROC) was 0.927. At a sensitivity of 90 percent the false positive rate was 18 percent.

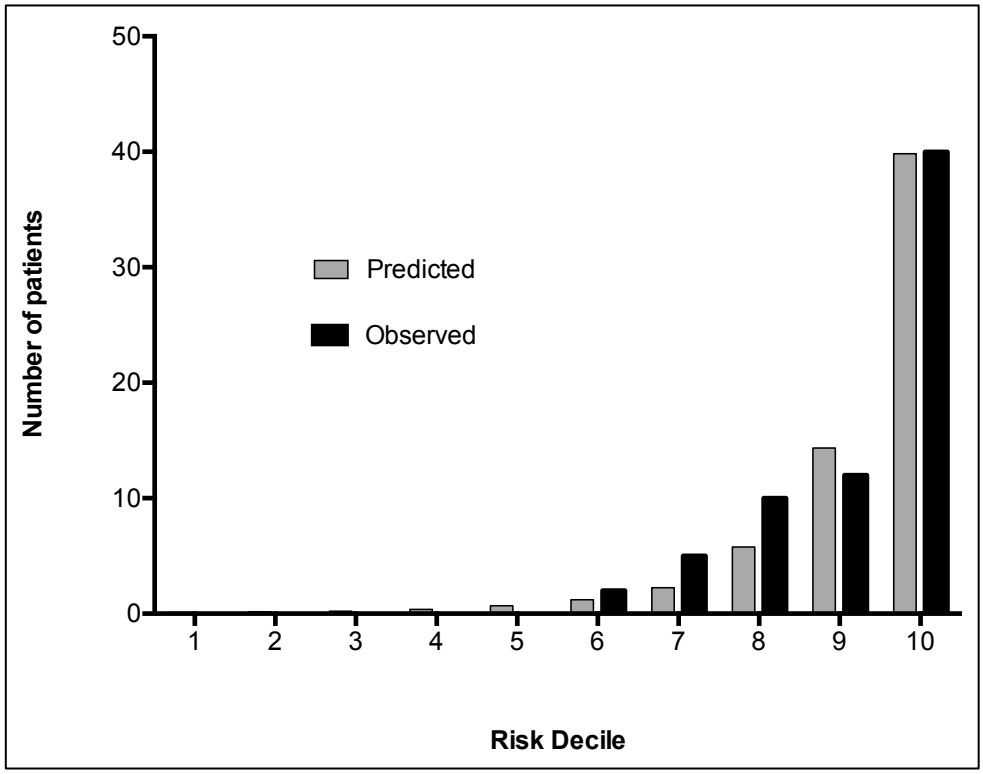


Figure 4.5: Model calibration in the development cohort. There was no significant difference between the predicted and observed frequency of coagulopathy in each risk group ($p = 0.3$).

4.4.6 Sensitivity analysis

All predictor variables contributed to the model's performance. Continuous variables related to hypoperfusion – specifically blood gas variables (Base Deficit, Lactate, pH), systolic blood pressure and heart rate – had the greatest impact on the models result (Figure 4.6).

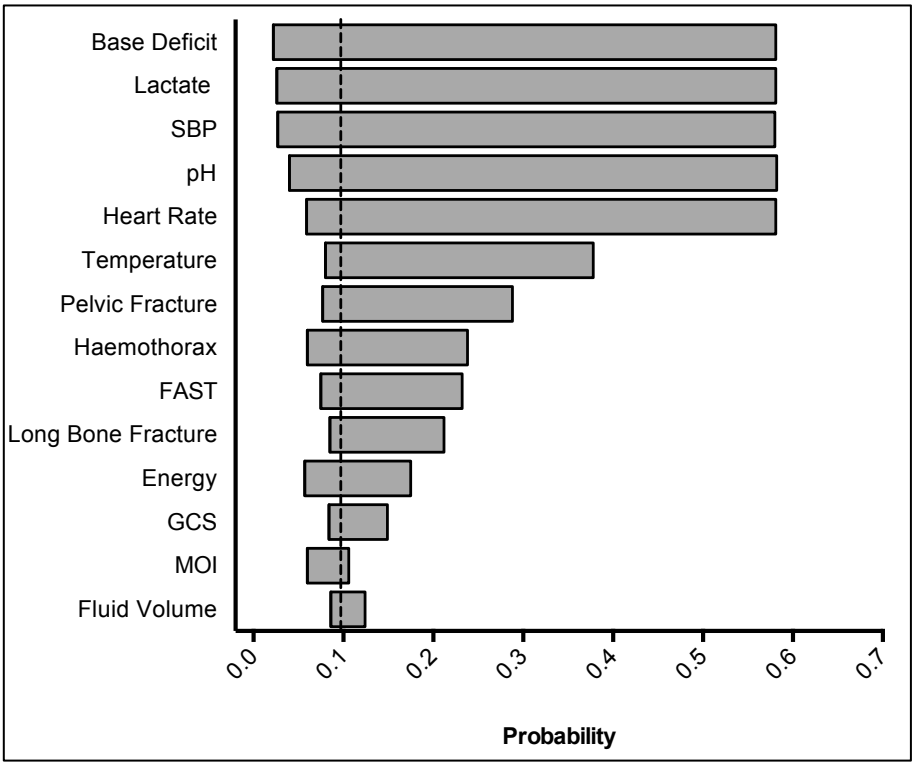


Figure 4.6: One-way sensitivity analyses of the impact individual predictor variables have on the models result.

4.4.7 Model presentation and application

A preview version of the complete model is available at http://valinor.agena.co.uk:8080/atcbn/atcbn.html. Entering predictor variable values allows the calculation of an individual patients probability of having traumatic coagulopathy. The tool is specifically designed to provide an individualised risk assessment that allows clinicians to exercise their own informed judgement and choice. The tool is not designed to predict decisions or prescribe treatments at a prespecified threshold.

This version of the model should not be used to inform clinical decisions until its performance in new patients has been adequately validated and the impact of predictions on decision-making and patient outcomes has been assessed.

4.4 Discussion

Key findings

A clinically relevant coagulopathy is common after traumatic injury and associated with significantly worse outcomes and greater consumption of health care resources. We have developed a model that can accurately predict Trauma Induced Coagulopathy from routine baseline findings. This early identification of coagulopathy has important implications for safe and effective trauma resuscitation, and efficient use of resources.

Benefits of early identification of coagulopathy

Early identification of coagulopathy enables early initiation of treatment. This is important because therapies that target Trauma Induced Coagulopathy, such as haemorrhage control (Gruen et al., 2012), tranexamic acid (Roberts et al., 2011), and haemostatic resuscitation with high ratios of blood products (Holcomb et al., 2013), are significantly more effective when initiated early. The benefit of specialist trauma care to patients with life-threatening injuries is also established (MacKenzie et al., 2006). Early identification, ideally in the pre-hospital phase, can be used to triage patients at risk of coagulopathy directly to specialist trauma centres capable of delivering optimal trauma care. Furthermore, pre-hospital identification of high-risk patients could be used to objectively activate in-hospital pathways and protocols, thereby minimising logistical delays in the provision of critical therapies such as blood component transfusions, emergency surgery, and interventional radiology. Indeed, pre-hospital activation of in-hospital major haemorrhage protocols has been shown to result in earlier access to haemostatic resuscitation and surgical haemorrhage control, and improved outcomes (Khan et al., 2013, Perkins et al., 2014).

Thus, a tool that accurately identifies patients at high-risk of coagulopathy, and that is used to accelerate access to optimal trauma care, has the potential to significantly improve trauma outcomes.

Early identification of coagulopathy also enables targeted treatment. Haemostatic resuscitation and abbreviated 'damage control' surgery procedures are life-saving interventions in the severely injured, but this benefit comes with a morbidity cost (MacLennan and Williamson, 2006, Watson et al., 2009, Johnson et al., 2010, Miller et al., 2005), and inappropriate use of these interventions may result in considerable and unnecessary harm (Mitra et al., 2012a, Hatch et al., 2011).

Accurate identification of patients that will benefit from a damage control approach is therefore essential to achieve optimal outcomes. The central physiological abnormality that defines the need for a damage control approach to resuscitation and surgery is the development of coagulopathy (Kashuk et al., 2010, Roberts et al., 2015). However, current haemostatic resuscitation strategies rely on blind, unguided protocols for blood component therapy. While these strategies improve blood product delivery and outcome in the coagulopathic patient, they expose patients with normal coagulation to unnecessary transfusion risk and may place an undue burden on hospital transfusion services.

Although coagulopathy is the key indication for damage control surgery, these procedures are almost always performed without any objective evidence of coagulation function. This is because it is not yet possible to identify coagulopathy within the optimal time frame available for damage control surgery decision-making. As a result, current DCS decisions rely on crude indicators of TIC (Roberts et al., 2015). Early and accurate identification of patients that will benefit from a damage control approach is essential for optimal outcomes, as delayed or inaccurate decisions may have major consequences for the patient. A model that allows early identification of patients at high-risk of coagulopathy could be used to identify patients most likely to benefit from the early

initiation of haemostatic resuscitation and damage control interventions, while minimising the risk of unnecessary harm in patients that are unlikely to derive any additional benefit.

Comparison with existing models

Two models have previously been developed to identify trauma patients with early coagulopathy (Cosgriff et al., 1997, Mitra et al., 2011). Cosgriff and colleagues (1997) derived a simple score from trauma registry data of patients who received a massive blood transfusion. They found that the increasing presence of four predictors (systolic blood pressure < 70mmHg, temperature < 34 °C, pH <7.1, and ISS > 25) directly correlated with the risk of developing coagulopathy, ranging from 1% (none present) to 98% (all four present). Their study was the first to demonstrate that early coagulopathy may be predictable from clinical information, and the authors suggest that their score may assist damage control surgery decision-making. This study, however, has a number of limitations that may impact its clinical relevance. Notably, one of the four variables in this score, ISS, is not known during the time frame the score is intended for use. Consequently, a subjective estimate of the ISS value would be required, which would affect the score's clinical reliability.

More recently, Mitra and colleagues (2011) developed a score from a large trauma registry database (n = 1680). Using regression analysis, they selected five predictors that are all available during the early phase of care (entrapment; systolic blood pressure < 100mmHg; temperature < 35 °C; suspected abdominal or pelvic injury; and chest decompression). At the suggested threshold, this Coagulopathy of Severe Trauma (COAST) score was able to identify 64 percent of patients with early coagulopathy and 95 percent of patients with normal coagulation in the development cohort.

The COAST score represents a number of improvements on Cosgriff's original score. Besides all the constituent variables being available at the intended time frame of use, the score was also developed from a substantially larger dataset, and the performance was prospectively validated in a new sample of patients.

However, neither of these scores is accurate enough to reliably support clinical decision-making (Brohi, 2011). The moderate predictive performance may be the result of a number of methodological limitations. Firstly, simple scores may not be sufficiently powerful to accurately predict complex pathophysiological processes. Second, by limiting the number of predictors and dichotomising continuous variables, much of the prognostic potential of available information is lost (Altman and Royston, 2006, Steyerberg et al., 2001). Lastly, although developed to predict patients with early coagulopathy, both scores actually predict a diagnostic test result. Using a surrogate outcome may affect the clinical relevance of the score (Grimes and Schulz, 2005).

Importance of predicting a relevant patient outcome

No matter how accurate a predictive model, it will have little clinical value if it is not developed to predict a relevant patient outcome. Coagulation dysfunction following trauma is a key outcome that precedes organ failure and death, and early identification provides an opportunity for effective intervention. However, the true state of the coagulation system cannot be directly observed and is therefore estimated using laboratory measures of coagulation function. The most widely used tests measure the clot formation time of plasma (PT, INR, APTT), but these measures have important limitations when used to estimate trauma coagulopathies. Furthermore, there is no clear measurement threshold for these tests that separate patients with normal coagulation from those with coagulopathy. As a result, current laboratory measures lead to some uncertainty in the diagnosis of coagulopathy.

Although developing a model that predicts laboratory test results is convenient, it is quite different from predicting the true coagulation state. A model developed to accurately predict the result of an imperfect laboratory test would need to replicate the measurement's diagnostic errors, further compounding uncertainty of the true state.

Additionally, even accurate models may predict a non-relevant threshold of the diagnostic test. For example, Cosgriff and colleagues (1997) developed a score to predict an early 'life-threatening' traumatic coagulopathy. This was defined as a Prothrombin Time and a Partial Thromboplastin Time more than twice the upper limit of normal laboratory controls. Although their score is able to identify patients that meet these criteria, the clinical relevance of this outcome is questionable. In their study population, there was no significant difference in mortality, emergency surgery, or blood transfusion requirements between patients classified as coagulopathic and those regarded as having normal coagulation (Table 4.5). Indeed, it could be argued that the majority of patients classified as normal in their study also required urgent haemostatic intervention and damage control surgery.

Table 4.5: Outcomes in 58 trauma patients who required a massive blood transfusion, according to a laboratory based classification of coagulopathy (Cosgriff et al., 1997). Traumatic coagulopathy was classified as a Prothrombin Time (PT) and a Partial Thromboplastin Time (PTT) of more than twice the upper limit of normal.

Outcome	Coagulopathy (n = 27)	Normal Coagulation (n = 31)	P - value
Mortality	12 (44.4)	13 (41.9)	1.0
Emergency Surgery	27 (100)	31 (100)	1.0
PRBC/24hr	26.2 ± 2.7	22.4 ± 1.9	0.24
FFP/24hr	13.9 ± 1.6	14.1 ± 1.9	0.90
Platelets/24hr	16.5 ± 3.1	15.8 ± 2.7	0.86

Data presented as number (%) or mean ± standard deviation.
PRBC/24hr, units of Packed Red Blood Cells transfused in 24 hours; FFP/24hr, units of Fresh Frozen Plasma transfused in 24 hours; Platelets/24hr, units of platelets transfused in 24 hours.

Scope of model

Although the model accurately predicts coagulopathy in the majority of injured patients, the scope of the model may be limited in certain circumstances. Firstly, although the models structure was learned from knowledge, the parameters were learned from ACIT data. The ACIT study is a prospective cohort study designed to investigate early coagulation changes following trauma and provides an optimal source of data for developing a model to predict traumatic coagulopathy. The model's performance, however, may not be accurate in populations excluded from the ACIT study. Injured patients on anticoagulation medication or those with significant liver disease were excluded from the ACIT study and the model is not designed to predict coagulation abnormalities resulting from these causes. Patients who could not be recruited into the ACIT study within two hours of injury were also excluded. The predominant causes of traumatic coagulopathy change during the clinical course, with exogenous causes having an increasing influence with time. Although the model includes predictors for all known causes of traumatic coagulopathy, the accuracy may be affected following prolonged periods of resuscitation.

Haemodilution with resuscitation fluids is an important iatrogenic cause of coagulopathy following trauma and the model is designed to predict coagulopathy following any volume of resuscitation fluid administration. However, patients who were administered more than two litres of intravenous fluid prior to recruitment were excluded from the ACIT study. ACIT data was used to learn the relationship for volumes less than two litres and published evidence was used to learn the relationship for higher volumes. Adequate published evidence of the relationship between increasing fluid administration and the development of coagulopathy exist. For example, Maegele et al. (2007) describe this relationship, stratified by injury severity, in an observational study of 8724 injured patients. The model's performance, however, was evaluated using ACIT data and therefore has not been validated in patients who received greater than two litres of prehospital fluid.

Secondly, during model development, subgroups of injured patients in which the model performed less well were identified. Although the model accurately predicts coagulopathy in the majority of patients with a head injury, it underestimates the degree of coagulopathy in patients with catastrophic head injuries. Indeed, patients with catastrophic head injuries account for over 80 percent of the model's false negative predictions. This subgroup of patients all had Head AIS scores of 5 with extensive intracranial bleeding and skull fractures. The majority had major abnormalities on CT imaging including signs of severely raised intracranial pressure, brain herniation, or pneumocephalus. Furthermore, these patients had no evidence of major extracranial bleeding or severe extracranial injuries (AIS > 3).

Coagulopathy is common following head injury and in patients with an isolated head injury, coagulopathy is more common in those with Traumatic Brain Injury (TBI) than those without (Zehtabchi et al., 2008). The mechanisms of coagulopathy following TBI are uncertain (Laroche et al., 2012). Classically, TBI coagulopathy was believed to be the result of systemic tissue factor release resulting in disseminated intravascular coagulation (Keimowitz and Annis, 1973). More recently, some investigators have argued that the mechanisms of traumatic coagulopathy in TBI patients are the same as in non-TBI patients: that TBI coagulopathy is primarily driven by tissue hypoperfusion and will not occur in its absence (Cohen et al., 2007). As the model is derived from existing knowledge, the incomplete understanding of the causes of coagulopathy in patients with isolated severe brain injuries is reflected in the model's performance in this subgroup of injured patients. The clinical value of accurately predicting coagulopathy in patients with catastrophic head injuries, however, is questionable, as these injuries have universally poor outcomes.

Patients who suffered an assault, with a relatively minor injury, but presented with a marked metabolic acidosis following extreme physical exertion, also resulted in some inaccurate predictions (false positive). In these patients the model was unable to

accurately differentiate the acute physiological changes resulting from decreased oxygen delivery in compensated haemorrhagic shock from those caused by increased oxygen requirements following extreme physical exertion. This is a common diagnostic difficulty in trauma care.

4.6 Strengths and Limitations

Strengths

This study has a number of strengths. Most important is that the model is developed to predict a key clinical outcome that is central to early therapeutic decision-making, and is not measurable during this time frame by any other methods. Second, the model's structure is developed from existing knowledge and represents an evidence-based understanding of traumatic coagulopathy. This is in contrast to traditional 'black-box' mathematical algorithms, which are the predominant prognostic modelling method in medicine. An evidence-based structure affords a number of potential advantages over traditional methods. These include improved face validity, which may lead to improved clinical credibility and user confidence, and reduced risk of data over-fitting that will enhance the models generalisability. Finally, data used for parameter learning was collected in a standardised way as part of a prospective cohort study, designed to assess early coagulation activation following injury. A prospective cohort study represents the optimal source of data for developing prognostic models, as this method should limit missing data and information bias.

Limitations

A Bayesian Networks predictive performance depends on how accurately its causal structure and network parameters approximate reality. The causal structure was informed by existing knowledge. However, our current understanding of the causes and

mechanisms of traumatic coagulopathy is incomplete. This may explain the model's underperformance in specific injury subgroups, such as patients with catastrophic head injuries, where knowledge of the mechanism of coagulopathy is weak. The excellent performance in the majority of injured patients, however, provides strong evidence that the understanding of the key causes of traumatic coagulopathy is accurate.

Network parameters were learned from data. How accurately these parameters estimate reality will depend on the quality of the data and how closely the study population represents the general trauma population. Data was collected using a standardised method as part of a prospective observational study, therefore limiting information bias. However, the study population came from a single Major Trauma Centre in a high-income country and this may affect the model's performance in other settings. The effect of this bias on the generalisability of the model may be minimal for two reasons. Firstly, the majority of parameters describe physiological relationships between variables that are unlikely to be influenced by the setting. And secondly, the most important component of the Bayesian network is the causal structure, which was derived from global knowledge of the condition. Ultimately, the generalisability of the model will need to be validated in new populations before clinical use.

The model is developed to predict a highly relevant clinical outcome and because of the importance of early identification of traumatic coagulopathy, we suggest that the model is operated at a highly sensitive threshold. Although the model has excellent predictive performance, it is not perfect, and the compromise for a high sensitivity is an increase in over-triage. As the majority of injured patients have normal coagulation, even a small increase in the over-triage rate will have a notable impact on the positive predictive value of the model. Furthermore, any over-triage rate will have both a clinical resource and cost impact. How acceptable this is, will need to be assessed under the conditions the model is intended for use.

CHAPTER FIVE

Validation of a Predictive Model for Trauma-Induced Coagulopathy

5.1 Introduction

A common problem in developing predictive models is over-fitting the model to the development data (Steyerberg, 2008). The result is an overly optimistic estimation of the models performance in the development population and weak performance in new patients. For this reason, validation of a model's predictive performance in a population that is different from the development population is an essential step before a model can be considered for clinical use (Altman et al., 2009, Steyerberg et al., 2013). Prognostic models are at particular risk of over-fitting when data-driven methods are used to determine the model structure, select predictors, and categorise predictors (Steyerberg, 2008). The risk is especially high when these methods are combined with small development datasets (Steyerberg et al., 2001).

The risk of over-fitting may be reduced if knowledge of the condition, rather than data, is used to derive the model structure and select predictors (Younesi and Hofmann-Apitius, 2013, Steyerberg et al., 2001). In addition to the potential for improved performance in new patients, integrating biomedical knowledge into predictive models may also improve face validity and user confidence. Knowledge-driven methods of developing predictive models are not well-described and, compared to data-driven methods, are labour intensive. As a result, integrating knowledge into predictive models is a challenging task and one that is seldom undertaken.

A second important limitation of traditional prognostic models is their inability to perform without a complete set of predictor information. This is especially relevant in emergency settings where incomplete and uncertain information is common. To be clinically useful, applications designed for emergency use should ideally be able to handle missing and uncertain predictor information. Advances in mathematical modelling have made it possible to develop models that can handle missing or uncertain predictor

information (Fenton and Neil, 2012b), however these techniques are not easily accessible and as a result there has been a slow adoption of these models in clinical practice.

In *Chapter Four*, we developed a model to predict Trauma Induced Coagulopathy (TIC) in the emergency setting. This condition is a key determinant of management strategies, health resource requirements, and outcome. The model was developed using Bayesian Networks, a technology capable of handling missing or uncertain information. Furthermore, to minimise over-fitting and enhance generalisability, the model was developed using a combination of knowledge and data-driven methods.

5.2 Study Aims

The overall aim of this study is to validate the model's predictive performance in an independent sample of injured patients.

The *first* objective was to validate the clinical relevance of the outcome that the model is developed to predict, in a new patient population.

Second, to validate the predictive performance of the model in a new patient population.

Third, to test the model's performance when predictor information is missing.

Last, to compare the models performance to that of accepted diagnostic blood tests, at predicting a clinically relevant coagulopathy.

5.3 Methods

5.3.1 Study design

This was a validation study for a TIC predictive model. Data from injured patients presenting directly to three Major Trauma Centres in Europe were used to assess the performance of the model.

5.3.2 Study population (validation cohort)

The Activation of Coagulation & Inflammation in Trauma (ACIT) study is a multi-national, prospective cohort study designed to identify the mechanisms by which the body's coagulation pathways are activated immediately following injury. Adult patients (>15 years) presenting directly to participating Major Trauma Centres, who meet local criteria for trauma team activation, are included. Exclusion criteria include: arrival in the emergency department > 2 hours after injury; prehospital administration of > 2000ml intravenous fluid; and burns covering > 5% of body surface area. Patients are retrospectively excluded if they decline consent, take anticoagulation medication, have moderate or severe liver disease, or a bleeding diathesis. The study was reviewed and approved by the National Research Ethics Committee of participating countries and written informed consent was obtained for all participants.

Two cohorts of injured patients enrolled in the ACIT study were used to validate the models ability to predict a clinically relevant coagulopathy. Both cohorts were independent of the model's development process and population. The temporal validation cohort consisted of consecutive patients enrolled in the London ACIT study following completion of model development (November 2011 to January 2014).

The external validation cohort consisted of consecutive patients enrolled into the ACIT study at two different trauma centres (John Radcliffe, Oxford, United Kingdom, and

Cologne-Merheim Medical Centre, Cologne, Germany) between January 2007 and January 2014.

5.3.3 Data collection

Data were prospectively collected on patient demographics, mechanism of injury, injury characteristics, prehospital and admission vital signs, prehospital fluid administration, primary survey findings, transfusion requirements in the first 24 hours of admission, surgery requirements, and outcome. Blood samples were collected immediately on hospital arrival and used for standard laboratory coagulation tests (PTr and APTT), thromboelastometry (ROTEM) and blood gas analysis. Anatomical injuries were described and classified by certified coders according to the AIS (Gennarelli, 2008) and Injury Severity Score (ISS) (Baker et al., 1974). Patients were followed-up daily until hospital discharge or death.

5.3.4 Outcome classification

The coagulation status of patients in the validation cohort was classified using the same method as described and used in *Chapter 4*. In brief, the steps were as follows:

1) All patients were classified according to the laboratory definition of acute traumatic coagulopathy, an admission PTr > 1.2.

2) Independently, all patients were classified using an expectation-maximisation algorithm based on the their admission clinical profile, PTr, Activated Partial Thromboplastin Time ratio (APTTr) and thromboelastometry (ROTEM, Pentapharm GmbH, Munich, Germany).

3) Cases where the laboratory and machine-learning methods agreed were assigned the corresponding coagulation state as their final classification.

4) Cases where the two methods disagreed, or the PTr sample had haemolysed, underwent expert review to determine a final classification.

Experts had no knowledge of the EM algorithm result or the structure of the prognostic model. Inter-reviewer agreement was evaluated with the kappa statistic and expert consistency was evaluated on a random sample of 30 patients with known coagulation status.

5.3.5 Clinical relevance of outcome

The clinical relevance of the coagulopathy classification was assessed in terms of mortality (24-hour mortality, in-hospital mortality); consumption of health care resources (blood transfusion, massive blood transfusion, and Damage Control Surgery (DCS) requirements); and number of days admitted to hospital (ITU length of stay, hospital length of stay) in the validation population.

5.3.6 Performance

The models prognostic performance was assessed in terms of discrimination, calibration and accuracy using multiple performance measures. Discrimination was assessed with the Receiver Operating Characteristic (ROC) curve, Area Under the ROC (AUROC) curve, sensitivity, and specificity. Calibration was evaluated using the Hosmer-Lemeshow test statistic (HL) and by visual assessment of the predicted and observed frequency of coagulopathy in 10 equal groups stratified by risk (Hosmer and Lemesbow, 1980). Accuracy was evaluated with the Brier Score (BS) and the Brier Skill Score (BSS) (Brier, 1950, Weigel et al., 2007). Performance in the temporal and external validation cohorts was compared to performance in the development cohort.

5.3.7 Sensitivity analyses

Individual predictors

The strength of the relationship between individual predictor variables and traumatic coagulopathy was calculated in the validation data. The AUROC was calculated for

continuous and ordinal predictor variables, and an Odds Ratio (OR) was calculated for binary predictor variables. This allowed an assessment of the relative importance of each predictor variable in the model. The AUROC for the complete model in the validation data and an OR for the complete model, using the threshold that achieved 90 percent sensitivity in the development data, were also calculated to allow comparison of individual predictor variables to the overall model.

Missing information

A major advantage of Bayesian Networks, compared to traditional prognostic models, is their ability to perform with missing or uncertain information. To assess the models sensitivity to missing information, the models overall performance in the validation data was compared to the performance when each predictor variable, in turn, was omitted as an input. Overall performance was also compared to the model's performance when clinically associated groups of variables, for example all blood gas variables (pH, lactate and base deficit), were omitted as inputs.

5.3.8 Comparison with diagnostic tests

The model's ability to identify injured patients with a clinically relevant coagulopathy was compared to laboratory (PTr) and rotational thromboelastometry (EXTEM CA5) diagnostic tests. The predictive model was operated at the threshold that achieved 90 percent sensitivity for traumatic coagulopathy in the development cohort. The diagnostic tests were operated at validated thresholds for identifying traumatic coagulopathy: a PTr > 1.2 (Frith et al., 2010) and a rotational thromboelastometry clot amplitude at 5 minutes of ≤ 35mm (Davenport et al., 2011). Both diagnostic tests were attempted in all validation patients.

5.3.9 Statistical Analysis

Normal-quartile plots were used to test for normality. Numerical data are reported as median with interquartile range (IQR) and categorical data as frequency (n) and percentage (%). The Mann–Whitney U test was used to compare numerical data and Fisher's Exact test was used to compare categorical data. Outcome comparisons between groups are reported as a Relative Risk (RR) with their corresponding 95 percent Confidence Intervals (CI). The time from injury to death between groups was compared with the log-rank (Mantel-Cox) test, and the results are presented as Kaplan-Meier curves. The area under ROC curves was calculated and compared using the method described by Hanley and McNeil (1982). The area under correlated ROC curves was compared using a non-parametric method that accounts for the paired test design (DeLong et al., 1988). Area under ROC curves are reported with their corresponding 95 percent CI. Inter-reviewer agreement for expert outcome classification was evaluated with the kappa statistic. Statistical analyses were performed using GraphPad PRISM v6 (GraphPad Software Inc., San Diego, CA, USA) and R statistical software (version 2.15.2). Statistical significance was set as a two tailed p-value of < 0.05.

5.4 Results

5.4.1 Baseline characteristics

The model's predictive performance was validated on a total of 491 patients recruited into the ACIT study at three specialist trauma centres in Europe. The temporal validation cohort consisted of 373 injured patients, of which 39 patients (10.5 percent) developed an acute coagulopathy. The external validation cohort consisted of 118 injured patients, of which fourteen patients (11.9 percent) developed coagulopathy. The baseline characteristics of the temporal and external validation cohorts had significant differences when compared to the development cohort (Table 5.1). The incidence of coagulopathy in the two cohorts, however, was similar ($p = 0.734$).

5.4.2 Clinical relevance of coagulopathy

Overall, 53 of the 491 injured patients in the validation population (10.8 percent) developed a coagulopathy. These coagulopathic patients had outcomes an order of magnitude worse than patients with normal coagulation (Table 5.2).

Mortality

In the first 24-hours following injury, the mortality rate was 24.5 percent in patients that developed a coagulopathy compared to 0.2 percent in patients with normal coagulation (RR: 11.07 (7.96 – 15.41); $P < 0.0001$).

In-hospital mortality was also substantially higher in coagulopathic patients compared to those with normal coagulation (49.1 percent versus 5.2 percent; RR: 8.69 (5.54 – 13.63); $P < 0.0001$). Injured patients in the validation cohort that developed a coagulopathy were significantly less likely to survive their injuries than those with normal coagulation, and the majority of deaths in coagulopathic patients occurred soon after injury (Figure 5.1).

Table 5.1: Baseline characteristics of the development and validation populations.

Characteristic	Missing Data (%)	Development cohort (N=600)	Validation cohort	
			Temporal (N=373)	External (N = 118)
Age – years (range)	<1	35 (16 – 95)	38 (16 – 93)	45 (16 – 92)§
Gender - male	0	486 (81.0)	309 (82.8)	78 (66.1)§
Mechanism of Injury - Blunt	0	475 (79.2)	299 (80.2)	116 (98.3)§
Pre-Hospital fluid (ml)	<1	0 (0 – 500)	0 (0 – 100)	100 (0 – 350)
Primary Survey findings:				
Respiratory Rate (bpm)[a]	2	20 (16 – 24)	18 (15 – 20)§	17 (14 – 22)
Heat Rate (bpm)	<1	95 (76 – 118)	87 (75 – 104)§	84 (74 – 108)§
Systolic Blood Pressure (mmHg)	2	130 (107 – 148)	134 (116 – 149)	136 (114 – 150)
Body Temperature (°C)	40	35.8 (35.1 – 36.5)	36.1 (35.7 – 36.7)§	36.0 (35.3 – 36.6)
Glasgow Coma Scale[a]	<1	15 (11 – 15)	15 (13 – 15)§	15 (10 – 15)
Suspected Haemothorax	<1	89 (14.9)	49 (13.2)	13 (11.1)
Suspected unstable pelvic fracture	<1	58 (9.7)	31 (8.3)	23 (19.5) §
Suspected long bone fracture	<1	132 (22.2)	89 (23.9)	28 (24.4)
FAST - Positive	<1	49 (8.2)	26 (7.0)	15 (12.7)
Baseline Blood Gas Analysis:				
pH	5	7.35 (7.30 – 7.40)	7.36 (7.31 – 7.39)	7.34 (7.25 – 7.39)
Lactate	6	2.1 (1.3 – 3.6)	2.3 (1.4 – 3.5)	2.6 (1.6 – 3.5)
Base Deficit	6	1.8 (-0.2 – 4.4)	0.6 (-1.5 – 3.3)§	1.6 (-0.7 – 5.1)
Baseline Thromboelastometry:				
EXTEM CA5 (mm)	8	44 (38 – 49)	44 (39 – 50)	46 (42 – 52)§
EXTEM MCF (mm)	8	61 (56 – 65)	63 (59 – 68)§	63 (57 – 68)§
FIBTEM MCF (mm)	8	14 (10 – 17)	15 (11 – 20)§	16 (11 – 20)§
Baseline laboratory values:				
INR	7	1.1 (1.0 – 1.1)	1.1 (1.0 – 1.1)§	1.0 (1.0 – 1.1)§
APTT (seconds)	7	23 (22 – 26)	23 (22 – 26)	27 (25 – 30)§
Haemoglobin (g/dL)	4	13.9 (12.4 – 14.9)	14.1 (12.9 – 15.0)§	13.7 (12.2 – 14.8)
Platelet count ($x10^9$ /L)	5	231 (193 – 272)	219 (182 – 264)§	245 (209 – 288)§
Injury severity:				
Injury Severity Score	2	16 (9 – 29)	13 (5 – 25)§	17 (9 – 29)
Head AIS ≥ 3	2	173 (28.8)	89 (25.9)	33 (28.0)
Chest AIS ≥ 3	2	257 (42.8)	106 (30.8)§	50 (42.4)
Abdomen AIS ≥ 3	2	62 (10.3)	44 (12.8)	15 (12.7)
Extremity AIS ≥ 3	2	198 (33.0)	100 (29.1)	52 (44.1)§

Data presented as number (%) or median (IQR) unless otherwise stated.

[a] Admission measurement or, if patient arrived intubated, pre-hospital measurement prior to sedation and intubation.

§ The characteristic differs significantly ($p < 0.05$) compared with the development cohort.

FAST, Focused Assessment with Sonography for Trauma; CA5, Clot Amplitude at 5 minutes; MCF, Maximum Clot Firmness; INR, International Normalised Ratio; APTT, Activated Partial Thromboplastin Time; AIS, Abbreviated Injury Score.

Consumption of health care resources

In the first 24-hours after injury, coagulopathic patients more frequently required a blood transfusion (96.2 percent versus 16.0 percent; RR: 77.98 (19.26 – 315.6); P < 0.0001) and a massive blood transfusion (47.2 percent versus 0.9 percent; RR: 14.22 (9.66 – 20.96); P < 0.0001) when compared to non-coagulopathic patients.

On average, each coagulopathic patient was transfused 9 (6 – 16) PRBC units and 8 (4 – 12) FFP units in the first 24 hours, compared to an average of 0 (0-0) units of either in patients with normal coagulation (P < 0.0001).

Coagulopathic patients were also more likely to require immediate DCS than non-coagulopathic patients (70.0 percent vs. 2.6 percent; RR: 20.6 (12.2 – 34.6); P < 0.0001).

Additionally, coagulopathic patients that survived had significantly longer critical care (14 (3 – 25) days versus 0 (0-1) days; p < 0.0001)) and hospital (30 (15 – 51) days versus 8 (2 – 20) days; p < 0.0001) length of stay, compared to survivors with normal coagulation.

Table 5.2: Comparison of outcomes and resuscitation requirements in 491 injured patients stratified by coagulation status.

Outcome	Missing Data (%)	Coagulopathy (N=53)	Normal Coagulation (N=438)	Risk Ratio (95% CI)	P -Value
Mortality:					
24-hour	0	13 (24.5)	1 (0.2)	11.1 (8.0 – 15.4)	< 0.0001
Hospital	0	26 (49.1)	23 (5.2)	8.7 (5.5 – 13.6)	< 0.0001
Emergency intervention in first 24 hours:					
Transfusion	0	51 (96.2)	70 (16.0)	78.0 (19.3 – 315.6)	< 0.0001
Massive transfusion	0	25 (47.2)	4 (0.9)	14.2 (9.7 – 21.0)	< 0.0001
DCS	10	35 (70.0)	10 (2.6)	20.6 (12.2 – 34.6)	< 0.0001

Data presented as number (%). Risk Ratios are for the coagulopathic group, as compared with the normal coagulation group. DCS, Damage Control Surgery

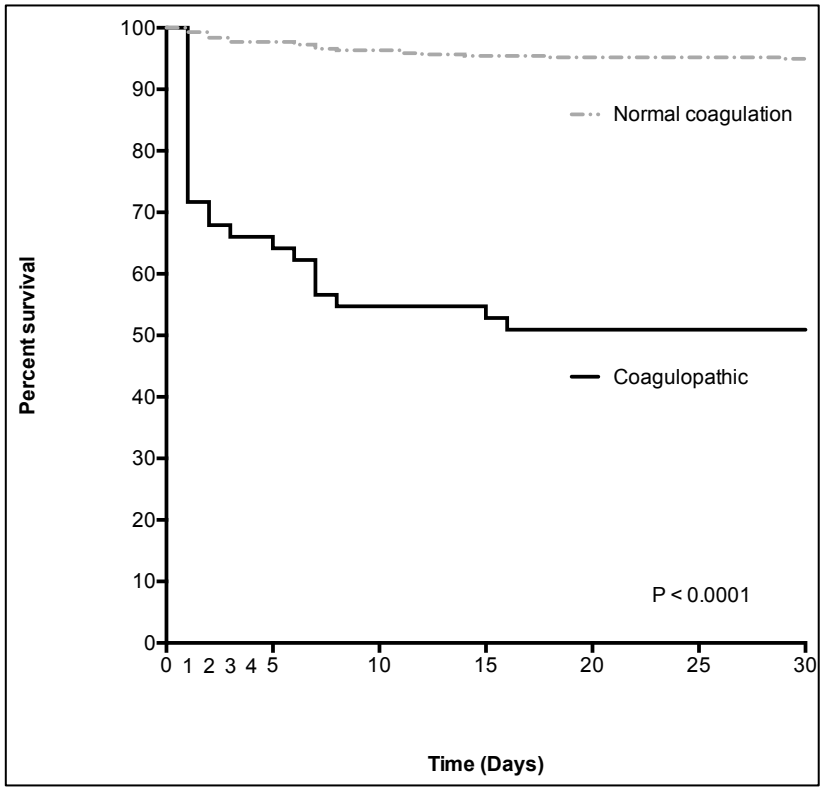


Figure 5.1: Kaplan-Meier estimates of the probability of survival for 491 injured patients with either normal coagulation or a coagulopathy. The P-value was calculated using the log-rank (Mantel-Cox) test.

5.4.3 Validation

The model maintained excellent predictive performance in the validation population (Figure 5.2). In the temporal validation cohort, the AUROC was 0.964 (0.941 – 0.987) and at a sensitivity set at 90 percent the specificity was 92 percent. The performance in the temporal cohort was significantly better than in the development cohort (0.964 (0.941 – 0.987) versus 0.927 (0.902 – 0.953); P = 0.03). In the external validation cohort, the AUROC was 0.927 (0.852 – 1.0) and at a sensitivity set at 90 percent the specificity was 84.5 percent. The model had similar performance in the external validation and development cohorts (AUROC 0.927 (0.852 – 1.0) versus 0.927 (0.902 – 0.953); P = 0.71). The model remained accurate and well calibrated in both validation cohorts (Table 5.3).

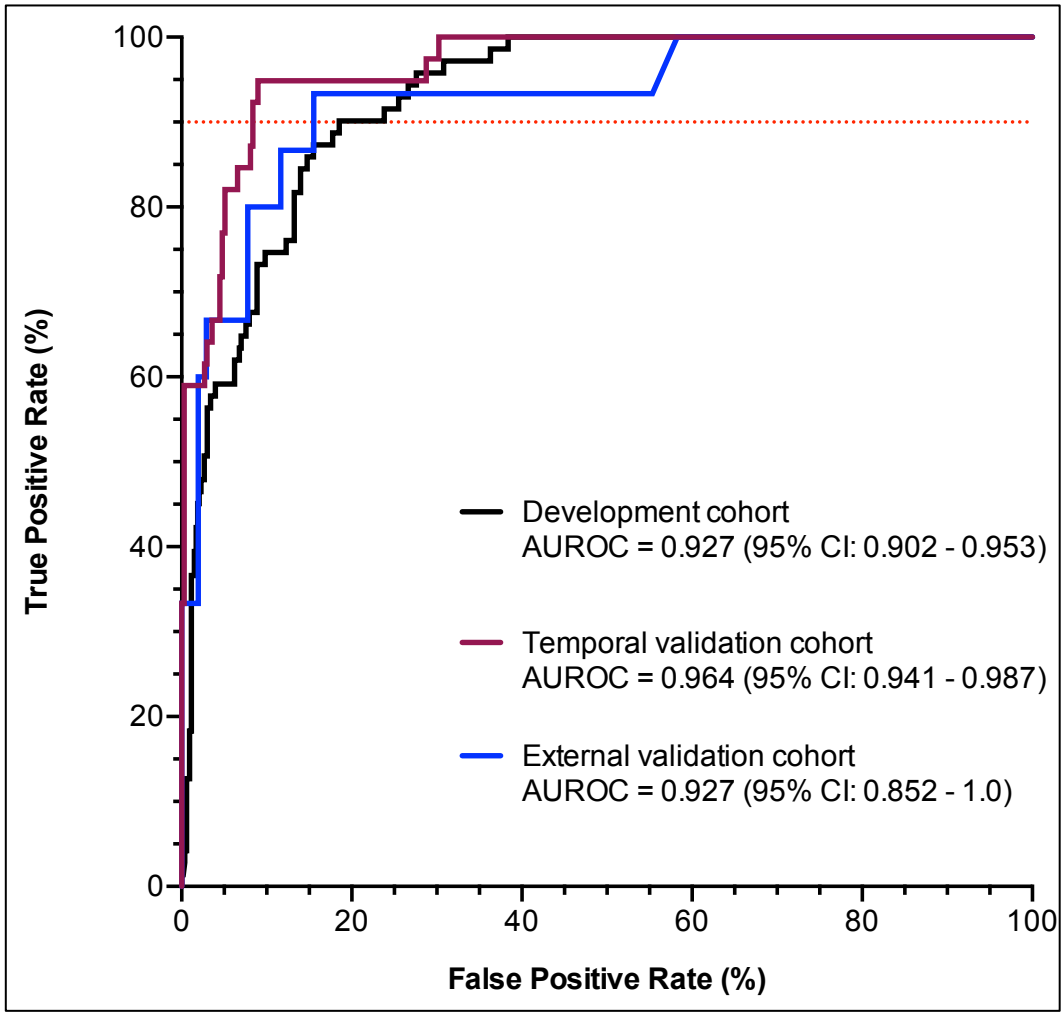


Figure 5.2: Accuracy of the trauma-induced coagulopathy predictive model in the development and validation cohorts. Accuracy was assessed using the Receiver Operating Characteristic (ROC) curve for coagulopathy predictions. This plots the true positive rate (sensitivity) against the false positive rate (1 – specificity). The red dotted line represents a true positive rate of 90 percent. At a true positive rate of 90 percent the false positive rate was 18, 8, and 15 percent for the development, temporal validation, and external validation cohorts respectively.

Table 5.3: Predictive performance measures for the trauma-induced coagulopathy model in the development, temporal validation, and external validation cohorts.

	Development	Validation Cohort	
Performance Measure	**Cohort**	**Temporal**	**External**
AUROC	0.927	0.964[a]	0.927
At 90% Sensitivity:			
Specificity	82 %	92 %	85 %
Positive Predictive Value	40 %	56 %	47 %
Negative Predictive Value	98 %	99 %	99 %
At 80% Sensitivity:			
Specificity	87 %	95 %	90 %
Positive Predictive Value	45 %	65 %	60 %
Negative Predictive Value	97 %	98 %	97 %
Hosmer-Lemeshow Statistic	9.3 (P = 0.32)	11.0 (P = 0.20)	8.7 (P = 0.37)
Brier Score	0.06	0.03	0.06
Brier Skill Score	0.39	0.53	0.38

[a] The performance differs significantly ($p < 0.05$) compared with the development cohort.
AUROC, Area Under the Receiver Operating Characteristic Curve.

5.4.4 Sensitivity Analyses

Individual predictors

The strength of the relationship between individual predictors included in the model and traumatic coagulopathy are shown in Figures 5.3 and 5.4. Blood gas variables were the strongest individual predictors of traumatic coagulopathy. The overall model, however, was a better predictor of traumatic coagulopathy than any individual variable in the model.

Missing information

The model's performance was not dependant on any individual predictors' information being available, and missing predictor information had minimal effect on the models overall performance. Sensitivity analyses, where each predictor variable in turn was omitted from the models inputs, did not demonstrate any significant effect on the models ability to predict traumatic coagulopathy (Fig 5.5). Indeed, the omission of all blood gas variable inputs, the three strongest individual predictors, had minimal effect on the model's predictive performance (overall performance: AUROC 0.952 (0.925 - 0.979) versus performance without blood gas information: AUROC 0.943 (0.911 – 0.976); P = 0.286).

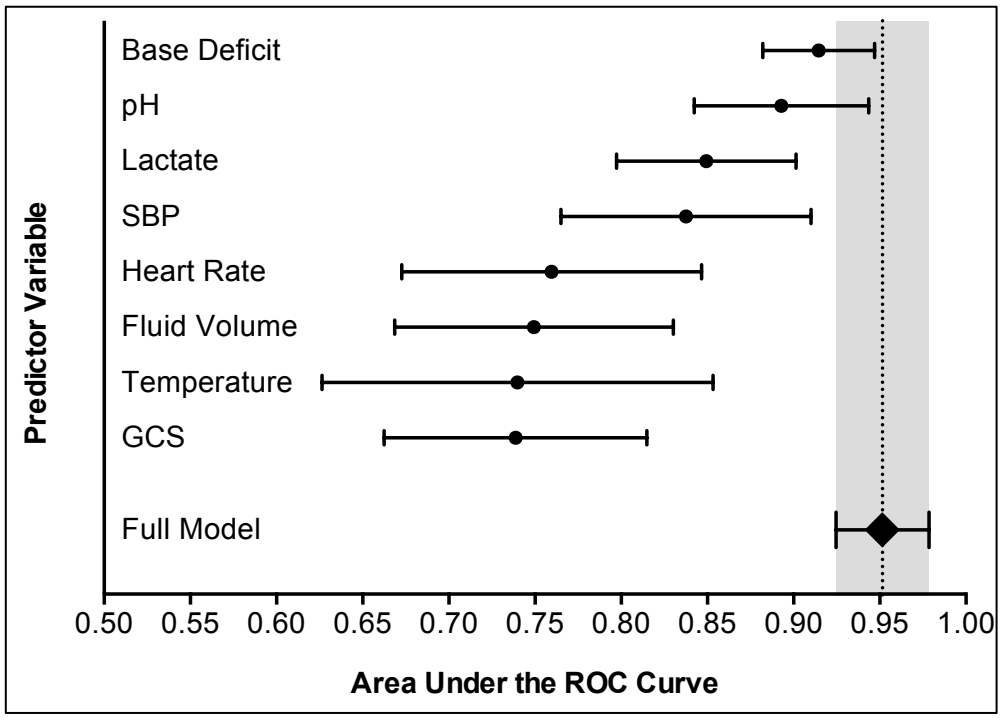


Figure 5.3: Area under the Receiver Operating Characteristic (ROC) curve with 95 percent Confidence Intervals for trauma-induced coagulopathy predictions in 491 injured patients using individual predictors and the full predictive model. The area under the ROC curve was calculated for each continuous and ordinal predictor in the model.

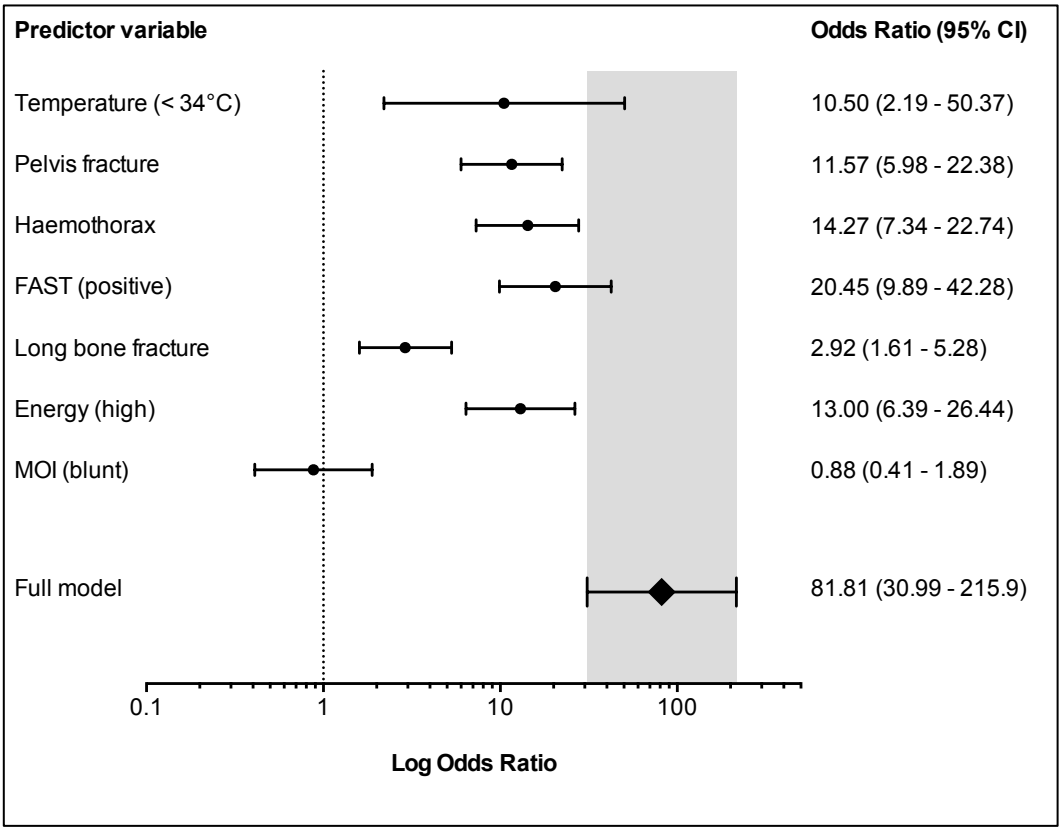


Figure 5.4: Odds Ratios with 95 percent Confidence Intervals (CI) for trauma-induced coagulopathy in 491 injured patients, according to individual predictors and the full predictive model. An Odds Ratio was calculated for each binary predictor in the model. The full model was operated at the threshold that achieved 90 percent sensitivity for traumatic coagulopathy in the development cohort. FAST, Focused Assessment with Sonography for Trauma; MOI, Mechanism Of Injury.

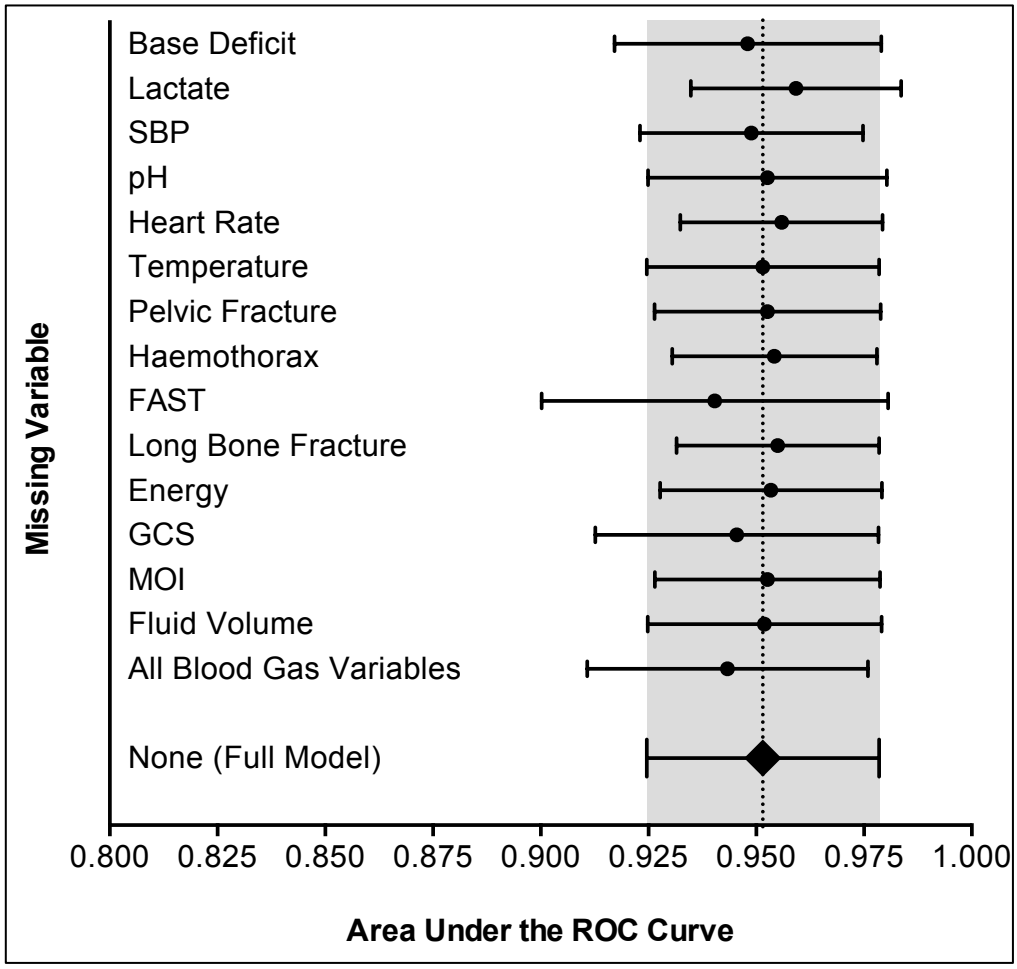


Figure 5.5: Performance of a Bayesian Network model at predicting trauma-induced coagulopathy in 491 injured patients when each of the models predictors, and all the blood gas variables, in turn, were omitted as inputs. Performance was measured by calculating the Area Under the Receiver Operating Characteristic (ROC) curve with 95 percent Confidence Intervals.

5.4.5 Comparison to diagnostic tests

The Bayesian Network model was able to calculate the probability of traumatic coagulopathy in all 491 injured patients in the validation population. At the designated operating threshold, the model identified 48 of 53 patients with traumatic coagulopathy. The accuracy of the models predictions was excellent, with an AUROC of 0.952 (0.925 - 0.979), sensitivity of 90.6 percent and specificity of 89.5 percent.

By comparison, a laboratory PTr result was available for 432 injured patients (88.0 percent). In three patients, clinicians were unable to obtain an admission blood sample, and in the remainder the sample haemolysed. A PTr > 1.2 identified 28 of 53 patients with traumatic coagulopathy. The diagnostic performance of the PTr test was an AUROC of 0.919 (95 percent CI: 0.873 – 0.965), sensitivity of 52.8 percent and specificity of 97.7 percent.

Rotational thromboelastometry (EXTEM CA5) provided a result for 420 patients (85.6 percent) and clot amplitude at 5 minutes ≤ 35mm identified 28 of the 53 patients with traumatic coagulopathy. The diagnostic performance of the EXTEM CA5 test was an AUROC of 0.853 (95 percent CI: 0.787 – 0.919), sensitivity of 52.8 percent and a specificity of 92.5 percent.

In the validation population, the Bayesian Network model had similar performance to PTr ($p= 0.175$) and significantly better performance than EXTEM CA5 ($p= 0.001$), at identifying injured patients with a clinically relevant trauma-induced coagulopathy.

5.5 Discussion

Key findings

Injured patients that present to hospital with an established coagulopathy have a formidable requirement for immediate resuscitative interventions and are responsible for almost all early trauma deaths. This study validates the clinical relevance of trauma-induced coagulopathy, and the excellent performance of a predictive model for this condition in new patients.

In addition, this study validates the ability of a Bayesian network to handle missing predictor information. The trauma-induced coagulopathy model's performance does not depend on any individual predictor, and accuracy is maintained with up to a fifth of predictor information missing. Furthermore, this study demonstrates that a Bayesian network predictive model can identify injured patients at risk of a clinically relevant coagulopathy with comparable accuracy to validated diagnostic tests, while overcoming many of the major limitations of these tests.

Implications of findings

The findings of this study have some important implications for trauma care and prognostic modelling. Perhaps the most important clinical implication is that the model can provide accurate and objective evidence of an individual patient's risk of coagulopathy. This is fundamental information for rational decisions on whether to activate, and use, damage control treatment strategies (Roberts et al., 2015, Holcomb et al., 2007a). Furthermore, the model provides rapid predictions using immediately available clinical information, thereby facilitating decisions at a time when treatment is most effective.

Immediate and aggressive damage control strategies improve survival in coagulopathic trauma patients (Stone et al., 1983, Rotondo et al., 1993, Holcomb et al., 2007a).

However, these strategies can cause considerable waste and harm if not indicated (Miller et al., 2005, Malone et al., 2003). Deciding on the appropriate use of damage control techniques, where the expected benefits outweigh the potential harms, can be difficult (Roberts et al., 2015). This is because decisions rely on the identification of patients at risk of coagulopathy, which is often uncertain at the time decisions need to be made. Diagnostic coagulation tests may reduce this uncertainty but are unhelpful in early decision-making as results are not available. Decisions are therefore based on clinical intuition. Although intuitive reasoning allows rapid decision-making, it is prone to error and has been shown to be unreliable in trauma patients, particularly at initial evaluation (Pommerening et al., 2015, Goettler et al., 2010). This validated model has the potential to provide meaningful support for early damage control decisions and reduce avoidable human errors associated with intuitive reasoning.

The model's ability to accurately predict coagulopathy, using clinical information only, and without the need for blood analysis, has particular relevance for trauma care in poorly resourced settings. Low- and middle-income countries bear the greatest burden of trauma morbidity and mortality, and a means to accurately identify high-risk patients enables triage and prioritising the utilization of scarce resources (WHO, 2014). In these settings, access to point-of care and laboratory diagnostic capabilities may be limited, but access to information technology is becoming widespread (Lewis et al., 2012). Clinical decision-support applications that use the Trauma-Induced Coagulopathy Bayesian Network may enable health care workers in these settings to provide timely and targeted haemostatic interventions, and improve the quality and consistency of trauma care.

In addition, the model can be used within trauma systems as a quality assurance tool to audit major haemorrhage protocol activations and damage control intervention decisions. The model may also be valuable for trauma research. It is an ideal tool for clinically

relevant risk categorisation and may also be used to select appropriate populations for efficient experimental studies on interventions for trauma-induced coagulopathy.

The findings of this study also have important implications for the methods used to develop prognostic models for use in emergency settings. This study supports the use of domain knowledge to reduce over-fitting and develop evidence-based models with better generalisability. An advantage of Bayesian networks is that they provide a platform that facilitates the incorporation of a broad range of evidence in model development (Yet et al., 2014a, Fenton and Neil, 2012b). Furthermore, this study demonstrates that Bayesian networks can produce robust models that are able to use a variable selection of predictor information, and capable of handling missing or uncertain information. This is likely to be a meaningful advantage in emergency settings, and overcomes a major limitation of traditional prognostic models, which require accurate and complete predictor information to function (Fenton and Neil, 2012b).

5.6 Strengths and limitations

Strengths

The Bayesian Networks predictive performance was validated in new patients presenting to three trauma centres in two countries. Each of the validation populations had significant differences to the development population, strengthening the validity of findings. Data was prospectively collected according to a standardised protocol, minimising the risk of information bias and missing information. Furthermore, the coagulation status of all patients was classified using a standardised method that overcomes the limitations of imperfect diagnostic tests and reduces the risk of measurement bias.

Limitations

This study has some limitations. First, the model's performance was validated in a civilian trauma population, where all patients were treated in well-resourced specialist trauma centres. The performance in military trauma populations and in less well-resourced settings is not known. The model, however, is designed to predict a pathophysiological response to trauma, prior to therapeutic intervention. While injury characteristics and the incidence of coagulopathy may differ in different settings, the mechanisms of Trauma Induced Coagulopathy remain constant, and the model is designed to take all known mechanisms into consideration. Furthermore, although different trauma systems may have a significant impact on the progression and outcome of coagulopathic patients, the trauma system itself will have minimal influence on an individual patients initial risk of developing coagulation derangements (Hess et al., 2008). Nonetheless, the model's performance in military and poorly resourced settings should be validated before use in these populations.

Second, the model is designed to enable early identification of coagulopathy risk to support rapid activation of targeted haemostatic interventions. The model was not designed to measure the response of the coagulation system to these interventions, and has not been validated for this purpose. Near-patient tests, such as thromboelastography, are able to describe specific coagulation function defects, and may be better suited to assess the response to therapy and tailor damage control interventions accordingly (Johansson et al., 2013).

Last, although the Bayesian network provides fundamental information to support rational damage control decisions, the impact of this information on decision-making, and ultimately patient outcomes, has not been assessed. Further research is warranted to examine the effect of using the model on clinical decisions, patient outcome, and cost-effectiveness of care, compared to standard trauma care.

CHAPTER SIX

Meta-analysis of Prognostic Factors for Amputation following Lower-Extremity Vascular Trauma

6.1 Introduction

6.1.1 Predicting limb viability

Once resuscitation is underway, the next step in the management of a patient with a severe lower limb injury is to decide whether limb salvage is possible. In some situations it may be clear that salvage is not an option. Examples of these situations include injuries where insufficient limb tissue remains for reconstruction, or injuries where the remaining tissue is clearly no longer viable. In the majority of cases, however, the decision may not be as obvious. In these cases, a comprehensive assessment of the wound should be performed in the operating theatre as soon as is possible after injury (NICE, 2016, Nanchahal J, 2009). Once the limb is reperfused and all contaminated and clinically non-viable tissue has been debrided, an assessment of the predicted viability and functional capacity of the remaining tissue is made. This information should be used by surgeons, and their patients, to make decisions on whether to pursue limb salvage or amputation.

The next two chapters describe the development of a prognostic model to help surgeons accurately predict limb viability. *Chapter Six* describes how potential prognostic factors were identified, and *Chapter Seven* describes the development and validation of the model.

6.1.2 Prognostic factors in Severe Lower Limb Trauma

A severe lower limb injury that involves Lower Extremity Vascular Trauma (LEVT) is a potentially devastating injury that may result in death, profound disability or limb loss (Kauvar et al., 2011, Tan et al., 2011, Mullenix et al., 2006). Management priorities are clear, foremost to save the patient's life and secondly to salvage the most functional limb possible (Feliciano et al., 2011, Scalea et al., 2012). Severe LEVT however, presents some of the most challenging decision-making in trauma surgery (Scalea et al., 2012, de Mestral et al., 2013).

Deciding between limb salvage and amputation is particularly complex with delayed or incorrect decisions leading to worse outcomes (*Chapter One*). Modern emergency surgery strategies aim to preserve all potentially viable tissue, thus allowing a window of opportunity for systematic wound assessment, patient counselling and early, informed decision-making (Glass et al., 2009, Nanchahal J, 2009). Good decisions rely on the ability to objectively estimate each treatments predicted outcome, ideally supplemented with both the patient's and surgical team's informed preference. Careful consideration of individual patient and injury prognostic factors is a central component of this decision-making process (de Mestral et al., 2013, Scalea et al., 2012, MacKenzie et al., 2002).

A number of prognostic factors for amputation have been described, including a traditional set comprising age, mechanism of injury (MOI), injury characteristics, duration of ischaemia, and presence of shock or compartment syndrome (MacKenzie et al., 2002, Scalea et al., 2012). These have been incorporated into numerous decision-support guidelines (ACS, 2005, Scalea et al., 2012) and scores (Gregory et al., 1985, Johansen et al., 1990, Russell et al., 1991, McNamara et al., 1994, Howe et al., 1987, Krettek et al., 2001, Rajasekaran et al., 2006). However, the supporting evidence for the majority of factors is weak and often conflicting, with prospective evaluation of existing scores failing to validate any clinically useful prognostic ability (Bonanni et al., 1993, Bosse et al., 2001, Durham et al., 1996). To improve decision-making and optimise outcome for these devastating injuries, an accurate understanding of prognosis and prognostic factors is required.

6.2 Study Aims

The overall aim of this systematic review is to develop a contemporary and more precise understanding of prognostic factors for amputation following surgical repair of LEVT. Our *first* objective is to estimate the overall risk of amputation following LEVT repair. *Second*, to identify potential patient, injury and treatment prognostic factors for amputation.

Last, to measure the strength of association between the identified prognostic factors and amputation.

6.3 Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). The review protocol was prospectively registered with PROSPERO (CRD42012002720) and is available at http://www.crd.york.ac.uk/PROSPERO/ (Appendix I).

6.3.1 Search Strategy

Relevant publications were identified by an electronic search of the MEDLINE, EMBASE and Cumulative Index of Nursing and Allied Health Literature (CINAHL) databases using combinations of the following keywords and Medical Subject Headings (MeSH) terms: "wounds and injuries", "amputation, traumatic", "leg injuries", "vascular system injuries", "iliac artery", "femoral artery", "popliteal artery" and "tibial arteries". The full MEDLINE search strategy is shown in Table 6.1. Search strategies were appropriately modified for EMBASE and CINAHL. Searches were limited to English language and human studies. Advances in trauma care and surgical techniques have improved limb salvage outcomes, therefore, to minimise historical outcome bias, searches were limited to publications after 01 January 2000. The last search was performed on 01 July 2012. Two authors independently screened the search output for potentially relevant citations, and then assessed the full-text of all identified citations for inclusion eligibility. Divergence was resolved by consensus through a third independent reviewer. The reference lists of included articles were manually searched for additional relevant publications.

Table 6.1: Full Medline search strategy.

Step	Search term
1.	exp "WOUNDS AND INJURIES"/
2.	exp AMPUTATION, TRAUMATIC/
3.	exp LEG INJURIES/
4.	OR/1-3
5.	exp ILIAC ARTEY/
6.	exp FEMORAL ARTERY/
7.	exp POPLITEAL ARTERY/
8.	exp TIBIAL ARTERIES/
9.	OR/5-8
10.	4 AND 9
11.	exp VASCULAR SYSTEM INJURIES/
12.	3 AND 11
13.	10 OR 12
Limits: Publication Year (2000 – 2012), Human and English Language.	
exp, explode.	

6.3.2 Eligibility Criteria

Observational studies reporting amputation rates for patients undergoing surgical repair of LEVT were included. Studies were excluded if they: (1) did not clearly report the population (surgical repair of LEVT) or outcome (secondary amputation) of interest, (2) only considered iatrogenic vascular injuries or chronic complications of vascular trauma, (3) only considered paediatric injuries, (4) contained less than five patients with LEVT or (5) only described non-standard surgical treatment or non-surgical treatment of vascular injuries.

6.3.3 Outcome Data

The primary outcome was amputation. This was defined as a major limb amputation, above the ankle, performed as a second procedure following an attempt at surgical reperfusion. Potential prognostic factors were identified from the included studies. All

patient, injury and treatment factors investigated in two or more studies were analysed, regardless of the reported strength of association.

6.3.4 Data Extraction

Two reviewers independently extracted methodological, population characteristic, prognostic factor and outcome data, using a piloted data extraction form (Appendix II). The following was extracted from each study: study design, number of patients, setting, level of trauma care, country of origin, publication year, duration of follow-up, number of limbs with surgically repaired LEVT, number of secondary amputations and the amputation rate in limbs with and without each identified prognostic factor. Study authors were contacted to obtain additional or missing prognostic information.

6.3.5 Definitions

Surgical repair was defined as any attempt to surgically restore blood flow to the distal lower extremity and included thrombectomy, primary repairs, interposition grafts and temporary shunt placement. Arterial injuries were catagorised into four zones according to anatomical level of injury: (1) Iliac, including common and external iliac arteries; (2) Femoral, including common, superficial and Profunda femoral arteries; (3) Popliteal; and (4) Tibial, including the tibio-peroneal trunk, anterior tibial artery, posterior tibial artery and peroneal artery. Multiple arterial injuries were catagorised by the most proximal level of injury requiring surgical repair. Mechanism of injury (MOI) was catagorised as blunt, blast, and penetrating, with penetrating injuries subdivided into those caused by gun shot wounds and those by stabbings. Primary studies dichotomised shock and soft tissue injury using differing thresholds. These prognostic factors were analysed according to the primary study categorisation. Primary study thresholds for shock included: Systolic Blood Pressure (SBP) < 90mmHg; SBP < 100mmHg; SBP < 90mmHg or Base Deficit > 6 mEq/ml or ≥ 4 units of Packed Red Blood Cells transfused in 24 hours (PRBC/24hr); and ≥ 10 units PRBC/24hrs. Primary study thresholds for soft tissue injury included:

Mangled Extremity Severity Score (MESS) (Johansen et al., 1990) soft tissue component ≥ 3; cases requiring reconstructive surgery techniques to achieve soft tissue cover and adjectives such as severe, extensive and major with clinical descriptors. Ischaemic time was dichotomised into less than or greater than six hours as this was the most common primary study threshold, calculable for all studies reporting this variable. Arterial repair was catagorised as primary repair (including thrombectomy, lateral repair, patch angioplasty and end-to-end anastomosis) and interposition graft, which was subdivided into those performed with autologous vein and those with prosthetic material. Venous injury treatment was dichotomised as ligation or repair.

6.3.6 Risk of bias

Risk of bias was assessed by individual sensitivity analysis of the following methodological factors: selection bias was assessed by analysing study design and sample size; performance bias was assessed by analysing the setting, level of trauma care, median year of study recruitment (< 2000 or ≥ 2000) and the economic development of the country according to the United Nations classification (2012); and attrition bias was assessed by analysing duration of follow-up (< 6 months or ≥ 6 months). Studies that did not report follow-up duration were catagorised as < 6 months for analysis. Primary outcome measurement bias was minimised by excluding studies that did not clearly define and report secondary amputation. To minimise prognostic factor measurement bias, only studies with objective categorisation and clear reporting were included in the analysis of individual prognostic factors. The quality of included studies was assessed using a framework proposed by Altman (2001). One point was available for each of eleven study features relating to the patient sample, intervention, follow-up, outcome, prognostic variables and analysis (Table 6.2). Risk of bias was assessed by a sensitivity analysis of the composite quality score (≥ median score or < median score). Publication bias was visually assessed with a funnel plot of effect size against sample size and statistically assessed with the Eggers test (1997).

Table 6.2: Criteria proposed by Altman (2001) used to score the methodological quality of included studies.

	Criteria
	Patient Sample
1.	Inclusion criteria defined?
2.	Sample selection explained?
3.	Baseline characteristics of sample described?
4.	Were participants a representative sample from a relevant population?
5.	Were all eligible patients included?
	Intervention
6.	Surgical intervention described?
7.	Staff, place and facilities appropriate for performing the intervention?
	Follow-up
8.	Sufficiently long (≥ 6 months for majority of sample)?
	Outcome
9.	Secondary amputation appropriately defined/described?
	Prognostic Variables
10.	Were important prognostic variables identified?
	Analysis
11.	Adjustment for confounding?
For each criteria, a 'yes' answer scores one point and an 'unsure' or 'no' answer scores zero. Maximum score is eleven and minimum zero.	

6.3.7 Statistical Analysis

Meta-analysis was performed using Bayesian Networks (Fenton and Neil, 2012b). A Bayesian approach to meta-analysis offers a number of advantages over the traditional frequentist approach (Sutton and Abrams, 2001). These advantages are particularly valuable in a meta-analysis of observational studies where heterogeneity, non-normal data distribution and zero event rates are expected. A Bayesian approach directly addresses these difficulties (Sutton and Abrams, 2001, Warn et al., 2002). The Bayesian Networks used in this study explicitly model between-study heterogeneity and within-study variability; do not assume normal data distribution; and do not require the addition

of a continuity factor for analyses when the event rate is zero. Moreover, a Bayesian approach allows the calculation of a 95 percent Credible Interval (CrI) and the ability to perform hypothesis tests using the entire posterior distribution of the parameter estimate. Such hypothesis tests with posterior probabilities addresses the clinical question more directly than conventional hypothesis tests with p-values (Burton et al., 1998).

A proportion and 95 percent CrI was calculated as the primary outcome in individual studies. These were pooled using a Bayesian random-effects model (Table 6.3). Using the same model, sensitivity analyses were performed to assess the risk of bias. Sub-group analyses were performed for each prognostic factor and both an absolute (proportion) and relative (Odds Ratio) measure of effect calculated. Odds Ratios could only be calculated in studies that reported outcomes for both the presence and absence of the potential prognostic factor. These were pooled using a similar Bayesian random-effects model (Table 6.3). Non–informative prior distributions for the pooled effects (mean: 0, variance: 1000) were used and uniform distributions (range: 0–2) for τ, the between-study standard deviation. For meta-analysis of odds ratios, the posterior probability (P) that the pooled estimate is greater than 1 was calculated. A P less than 10 percent is considered strong evidence of protective effect and P greater than 90 percent, strong evidence of harmful effect (Aitkin et al., 2009). Heterogeneity was reported as the I^2 statistic. Inter-reviewer agreement for inclusion eligibility was evaluated with the kappa statistic. Statistical analyses were performed using AgenaRisk software (Agena, London, UK).

Table 6.3: Bayesian Network models for A) Proportions and B) Odds Ratio meta-analysis.

A) Proportions
$r_i \sim Bin(p_i, n_i)$ $logit(p_i) = \mu_i$ $\mu_i \sim N(\delta, \tau^2)$ $\delta \sim N(0,1000)$ $\tau \sim Unif(0,2)$
B) Odds Ratio
$r_{1i} \sim Bin(p_{1i}, n_{1i})$ $r_{2i} \sim Bin(p_{2i}, n_{2i})$ $logit(p_{1i}) = \mu_i$ $logit(p_{2i}) = \mu_i + \delta_i$ $\delta_i \sim N(\delta, \tau^2)$ $\delta \sim N(0,1000)$ $\tau \sim Unif(0,2)$

6.4 Results

6.4.1 Search results and characteristics of included studies

Overall, 45 studies were included (Figure 6.1). There was near perfect agreement between reviewers on study eligibility (κ = 0.96 [95 percent CI: 0.92 – 1.0]). Two hundred and seven studies were excluded because of an ineligible study type: narrative review (91), case report (66), case series ≤ 5 (46) and systematic review (4). Forty-eight studies were excluded because of an ineligible study population: no acute lower limb vascular trauma (19), vascular injuries not described (21) and surgery either not performed, described or standard practice (9). Thirteen studies were excluded because amputation outcome was not reported (4) or secondary amputation was not defined (9). The authors of 27 included studies were contacted for additional or missing prognostic information, eleven replied and six provided unpublished original data (Davidovic et al., 2005, Fox et al., 2010, Perkins et al., 2012, Burkhardt et al., 2010, Woodward et al., 2008, Dar et al., 2003). Characteristics of the included studies are presented in Table 6.4.

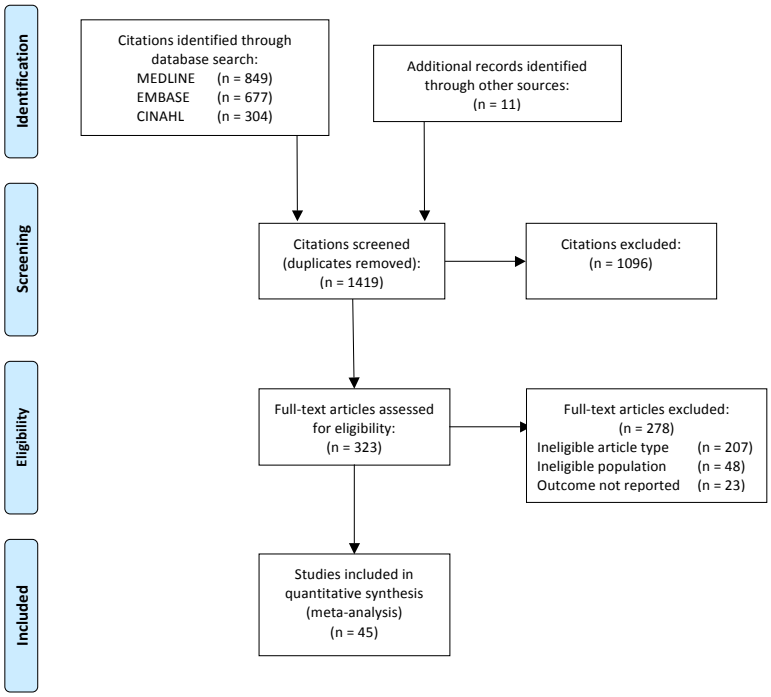


Figure 6.1: PRISMA flow chart of study selection process.

6.4.2 Secondary amputation rate

The 45 included studies described a total of 3168 patients who underwent surgical LEVT repair in 3187 discrete lower limbs. Three hundred sixty nine limbs underwent secondary amputation. The pooled secondary amputation rate was 10.0 (95 percent CrI: 7.4 to 13.1) percent (Figure 6.2).

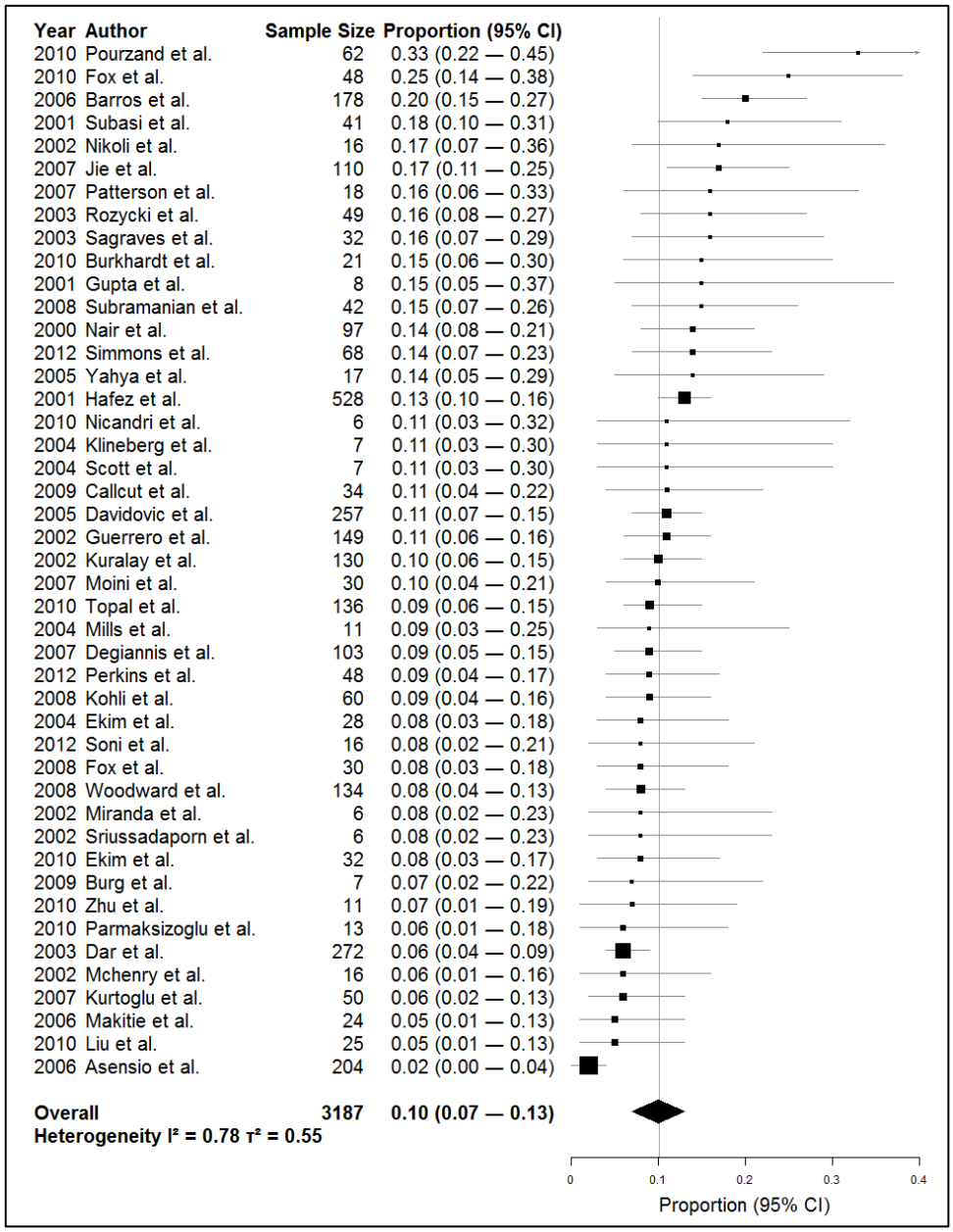


Figure 6.2: Forest plot of secondary amputation proportions for included studies. Overall pooled proportion and heterogeneity, calculated using a Bayesian random-effects hierarchical model, is presented.

Table 6.4: Clinical and methodological characteristics of included studies.

Reference	Population	Setting	Specialist Trauma Care	Country	Median study year	Study design	Sample Size	2° Amp	Quality Score	Average follow-up duration (months)
Pourzand et al. (2010)	Blunt Popliteal AI with associated fracture	C	Yes	Iran	2007	R	62	23	8	16
Fox et al. (2010)	Popliteal AI with associated shock	M	Yes	Iraq	2004	R	48	14	8	48*
Barros D'Sa et al. (2006)	Lower limb AI	C	No	Northern Ireland	1984	R	178	38	7	-
Subasi et al. (2001)	Popliteal AI with associated fracture/dislocation	C	No	Turkey	1992	R	41	9	7	-
Nikoli et al. (2002)	Penetrating lower limb AI with associated fracture	M	No	Yugoslavia	1993	R	16	4	6	-
Jie et al. (2007)	Lower limb AI with associated fracture	C	No	China	1982	R	110	20	6	25*
Patterson et al. (2007)	Lower limb AI with associated dislocation	C	Yes	US	1995	P	18	4	8	24*
Rozycki et al. (2003)	Blunt lower limb Ai	C	Yes	US	1998	R	49	9	7	-
Sagraves et al. (2003)	Popliteal AI	C	Yes	US	1997	R	32	6	9	-
Gupta et al. (2001)	Popliteal AI	C	Yes	Australia	1996	R	8	2	8	-
Burkhardt et al. (2010)	Tibial AI	M	Yes	Iraq / Afghanistan	2005	R	21	4	10	39*
Subramanian et al. (2008)	Lower limb AI	C	Yes	US	2002	R	42	7	8	-
Yahya et al. (2005)	Popliteal AI	C	No	Australia	1998	R	17	3	9	-
Simmons et al. (2012)	Lower limb AI	C	Yes	US	2002	R	68	10	8	-

AI, Arterial Injury; C, Civilian; M, Military; Mix, both civilian and military; 2° Amp, secondary amputation; -, not stated; *, minimum follow-up ≥ 6 months

Table 6.4: Clinical and methodological characteristics of included studies (continued).

Reference	Population	Setting	Specialist Trauma Care	Country	Median study year	Study design	Sample Size	2° Amp	Quality Score	Average follow-up duration (months)
Nair et al. (2000)	Penetrating Popliteal AI	C	Yes	South Africa	1990	R	97	14	8	-
Nicandri et al. (2010)	Lower limb AI with associated dislocation	C	No	US	2004	R	6	1	6	-
Scott and Hirshberg (2004)	Popliteal AI	C	Yes	US	n/a	R	7	1	4	-
Klineberg et al. (2004)	Popliteal AI with associated dislocation	C	Yes	US	1995	R	7	1	8	-
Hafez et al. (2001)	Lower limb AI	C	Yes	South Africa	1991	R	528	68	9	-
Callcut et al. (2009)	Popliteal AI	C	Yes	US	2000	R	34	4	10	14
Mills et al. (2004)	Lower limb AI with associated dislocation	C	Yes	US	2000	P	11	1	9	12*
Moini et al. (2007)	Popliteal AI with prolonged ischaemia	C	No	Iran	2003	R	30	3	8	12*
Guerrero et al. (2002)	Lower limb AI	C	Yes	US	1991	R	149	16	10	-
Davidovic et al. (2005)	Lower limb AI	Mix	No	Serbia	1996	R	257	28	9	-
Kuralay et al. (2002)	Lower limb AI	C	No	Turkey	1995	R	130	13	6	74*
Soni et al. (2012)	Lower limb AI with associated fracture	C	Yes	UK	2000	R	16	1	7	60*
Topal et al. (2010)	Lower limb AI	C	No	Turkey	2005	R	136	13	9	> 12*
Perkins et al. (2012)	Lower limb AI	C	Yes	UK	2008	R	48	4	9	-
Ekim et al. (2004)	Lower limb AI	C	No	Turkey	2001	R	28	2	7	> 6*
Kohli and Singh (2008)	Lower limb AI	C	No	India	1998	R	60	5	6	< 1
Degiannis et al. (2007)	Penetrating lower limb AI from GSW	C	Yes	South Africa	2002	R	103	9	5	< 6

AI, Arterial Injury; C, Civilian; M, Military; Mix, both civilian and military; 2° Amp, secondary amputation; -, not stated; *, minimum follow-up ≥ 6 months

Table 6.4: Clinical and methodological characteristics of included studies (continued).

Reference	Population	Setting	Specialist Trauma Care	Country	Median study year	Study design	Sample Size	2° Amp	Quality Score	Average follow-up duration (months)
Fox et al. (2008b)	Lower limb AI with associated shock	M	Yes	Iraq / Afghanistan	2006	R	30	2	9	< 1
Sriussadaporn and Pak-art (2002)	Popliteal AI with associated dislocation	C	No	Thailand	1997	R	6	0	8	6*
Miranda et al. (2002)	Lower limb AI	C	Yes	US	1995	P	6	0	8	19*
Ekim and Odabasi (2010)	Femoral AI	C	No	Turkey	2004	R	32	2	5	1.5
Burg et al. (2009)	Penetrating lower limb AI	C	No	Israel	2004	R	7	0	7	-
Woodward et al. (2008)	Penetrating Femoral – Popliteal AI	M	Yes	US	2006	R	134	10	6	-
Zhu et al. (2010)	Popliteal AI	C	No	China	2003	R	11	0	5	-
Kurtoglu et al. (2007)	Lower limb AI	C	No	Turkey	2002	P	50	2	7	18*
Dar et al. (2003)	Popliteal AI	M	No	India	1994	R	272	16	9	-
Parmaksizoglu et al. (2010)	Lower limb AI with associated fracture	C	No	Turkey	1999	R	13	0	6	> 6*
McHenry et al. (2002)	Penetrating lower limb AI with associated fracture	C	Yes	US	1995	R	16	0	7	-
Makitie et al. (2006)	Penetrating lower limb AI	C	No	Finland	1995	R	24	0	6	-
Liu et al. (2010)	Lower limb AI with associated fracture	C	No	China	2008	R	25	0	6	-
Asensio et al. (2006)	Femoral AI	C	Yes	US	1997	R	204	0	8	-

AI, Arterial Injury; C, Civilian; M, Military; Mix, both civilian and military; 2° Amp, secondary amputation; -, not stated; *, minimum follow-up ≥ 6 months

6.4.3 Heterogeneity

Heterogeneity between included studies was responsible for a large proportion of the total variability in study outcomes (Figure 6.2). The majority of heterogeneity was clinical, arising from differences in study populations and consequential distribution of prognostic factors (Figure 6.6). Differences in study methodology had minimal effect on study outcome variability (Figure 6.3).

6.4.4 Risk of bias

Sensitivity analyses did not identify any significant risk of selection, performance or attrition bias (Figure 6.3). Secondary amputation was appropriately defined and measured in all included studies, limiting the risk of measurement bias. The median quality score of included studies was 8 (range: 4 to 10) out of a maximum 11. Sensitivity analysis of studies with a ‘low’ and ‘high’ score did not identify any significant risk of bias. There was no evidence of publication bias. Visual inspection of a funnel plot (Figure 6.4) and Eggers test ($p = 0.204$) showed no significant asymmetry.

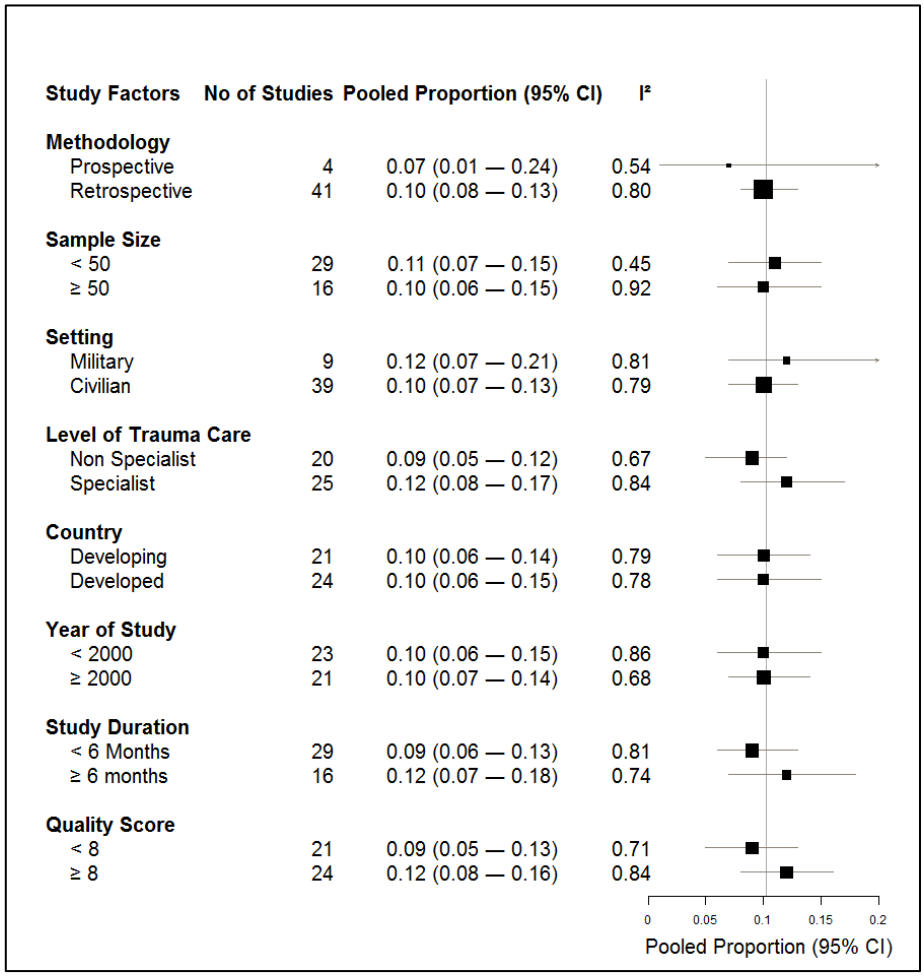


Figure 6.3: Sensitivity analyses of methodological differences between included studies.

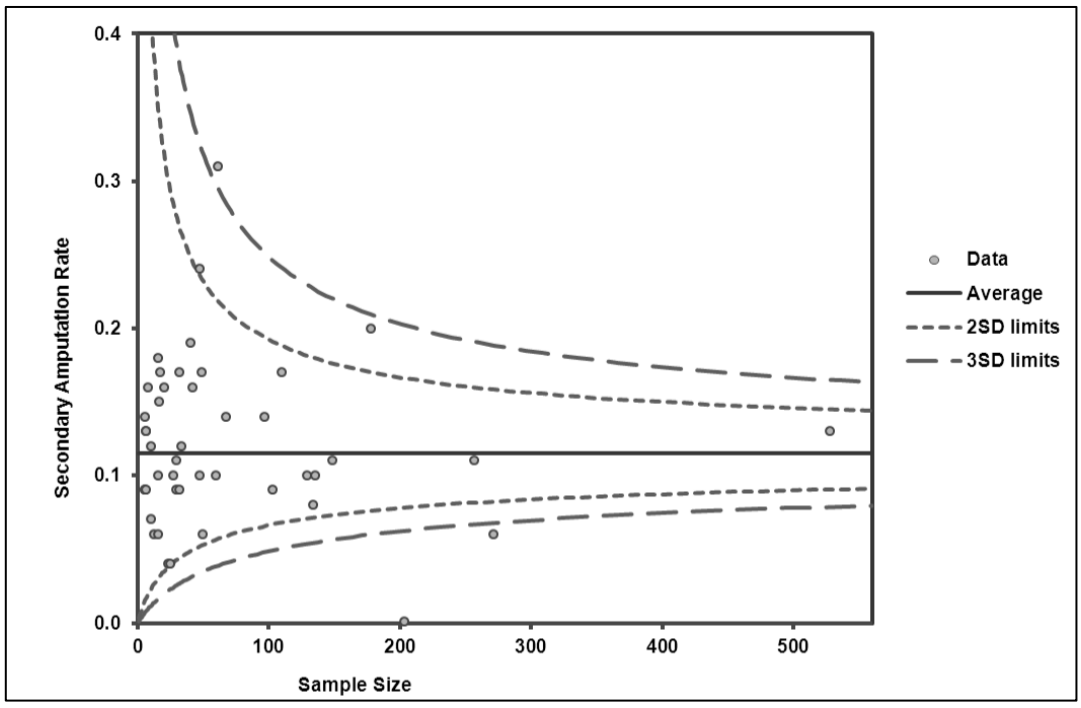


Figure 6.4: Funnel plot of effect size against sample size for 45 included studies.

6.4.5 Prognostic factors for secondary amputation

The included studies described 15 potential prognostic factors for secondary amputation (Figure 6.5). Two thirds (10/15) of these prognostic factors had conflicting evidence supporting their association with amputation. Four prognostic factors (age, gender, associated nerve injury, method of arterial repair) had no evidence to support a significant association with amputation, while compartment syndrome was the only factor where all studies reporting its effect showed a significant association with amputation.

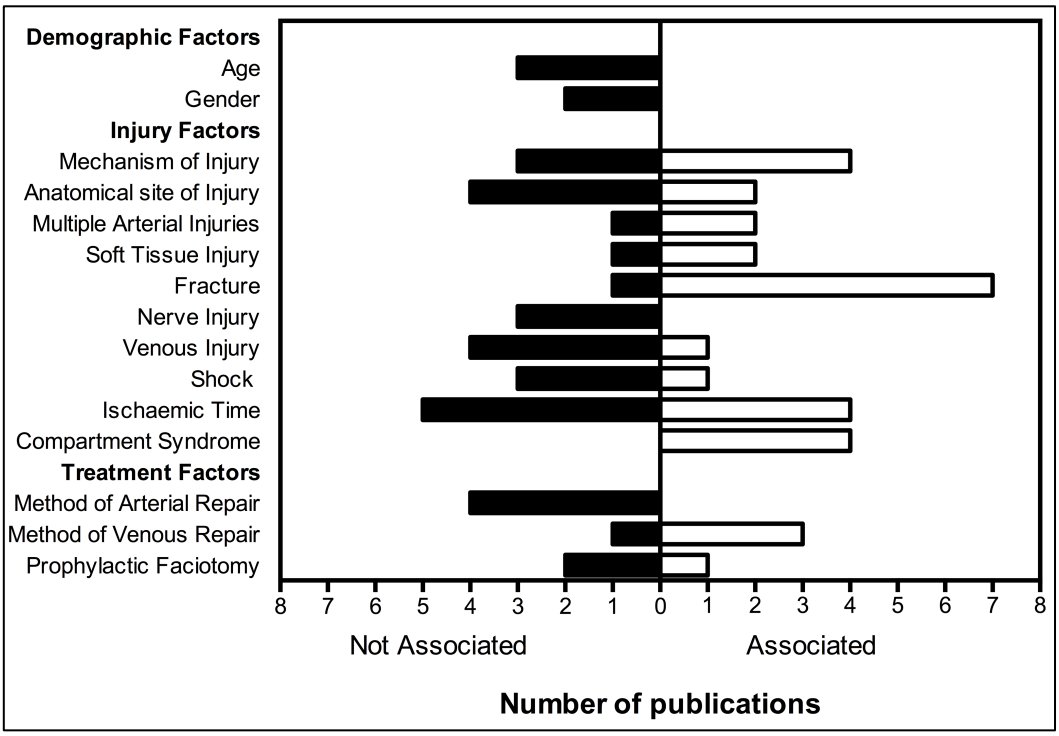


Figure 6.5: Potential prognostic factors identified from the included studies and the evidence supporting an association with secondary amputation (2000 to 2012).

6.4.5.1 Patient factors

Age was poorly reported and could only be analysed in 12 studies describing 577 patients (Table 6.5). Four studies (Davidovic et al., 2005, Gupta et al., 2001, Mills et al., 2004, Perkins et al., 2012) described patients older than 55 years and a higher amputation rate was observed in this population (Figures 6.6 and 6.7). Gender was adequately reported in 18 studies describing 1809 patients (Table 6.5). Females had a small but significantly higher risk of secondary amputation than males (Figures 6.6 and 6.7).

6.4.5.2 Injury factors

Mechanism of Injury

MOI was reported in 41 studies describing 2813 injured limbs (Table 6.5). The risk of secondary amputation increased with a higher energy MOI: penetrating (5 percent), blunt (16 percent), blast (19 percent) (Figures 6.6 and 6.7). In 31 studies, penetrating MOI was further divided into those resulting from gun shot wound's (1176 limbs, 96 secondary amputations) and stab wounds (207 limbs, 4 secondary amputations). Vascular injury resulting from GSW's had a higher risk of secondary amputation than those resulting from stab wounds (0.06 [95 percent CrI: 0.02 – 0.10] versus 0.01 [95 percent CrI: 0.0 – 0.04]); OR 1.3 [95 percent CrI: 0.27 – 3.2]; P = 0.59).

Anatomical site of Injury

The anatomical site of the arterial injury was clearly reported in 41 studies describing 2859 injured limbs (Table 6.5). Vascular repair of femoral artery injuries had the lowest risk of secondary amputation (4 percent), while repairs of popliteal (14 percent) and iliac arteries (18 percent) were associated with substantially higher risk (Figures 6.6 and 6.7).

The presence of additional arterial injuries at multiple anatomical levels was specifically reported in 17 studies describing 1205 limbs (Table 6.5). Patients injured at multiple arterial levels had 5-times the risk of secondary amputation when compared to those with single level injuries (Figures 6.6 and 6.7).

Associated Injuries

The presence or absence of associated limb injuries was clearly reported in 32 studies describing 2416 injured limbs for fractures and knee dislocations; 24 studies describing 2303 limbs for venous injuries; and 12 studies describing 1384 limbs for nerve injuries (Table 6.5). The degree of soft tissue injury was reported in 18 studies describing 1015 patients (Table 6.5). Primary studies classified a significant soft tissue injury using: clinical descriptors (Fox et al., 2010, Gupta et al., 2001, Kuralay et al., 2002, Pourzand et al., 2010, Topal et al., 2010, Fox et al., 2008b, Dar et al., 2003); the MESS score (Callcut et al., 2009, Guerrero et al., 2002, McHenry et al., 2002, Yahya et al., 2005); as injuries necessitating reconstructive techniques to achieve soft tissue cover (Subasi et al., 2001, Soni et al., 2012, Parmaksizoglu et al., 2010) and confirmation of no soft tissue defect (Mills et al., 2004, Miranda et al., 2002, Nicandri et al., 2010, Patterson et al., 2007). A significant soft tissue injury was associated with a six-fold increase in amputation while the presence of a fracture was associated with a four-fold increase. An additional venous or nerve injury was not associated with a substantial increase in amputation risk (Figures 6.6 and 6.7).

Injury complications

Shock, prolonged ischemia (> 6 hours), and compartment syndrome were clearly reported in nine studies describing 792 patients, 16 studies describing 1052 limbs and ten studies describing 1341 limbs respectively (Table 6.5). Prolonged ischaemia and the development of compartment syndrome were associated with a four- and five-fold

increase in the risk of secondary amputation. Admission shock was not associated with a significant increase in secondary amputation (Figures 6.6 and 6.7).

6.4.5.3 Treatment factors

Arterial repair

The surgical method of arterial injury repair was clearly reported in 28 studies describing 2025 vascular injuries (Table 6.5). Injuries that required an interposition graft had twice the risk of secondary amputation when compared to injuries that underwent primary repair (Figures 6.6 and 6.7). The method of interposition graft was further sub-divided in 26 studies describing 1184 injuries. Injuries repaired with a prosthetic interposition graft had a higher risk of secondary amputation than those repaired with reversed autologous vein (0.17 [95 percent CI: 0.05 – 0.38] versus 0.10 [95 percent CI: 0.06 – 0.15]; OR 1.88 [95 percent CI: 0.55 – 5.825); P = 0.88).

Venous repair

The management of 904 associated venous injuries was reported in 21 studies (Table 6.5). The risk of secondary amputation was six times lower following venous repair than venous ligation (Figures 6.6 and 6.7).

Prophylactic fasciotomy

The use of prophylactic faciotomies was reported in 12 studies describing 971 injured limbs (Table 6.5). The proportion of patients undergoing secondary amputation was similar in cohorts that did and did not have prophylactic faciotomies (Figures 6.6).

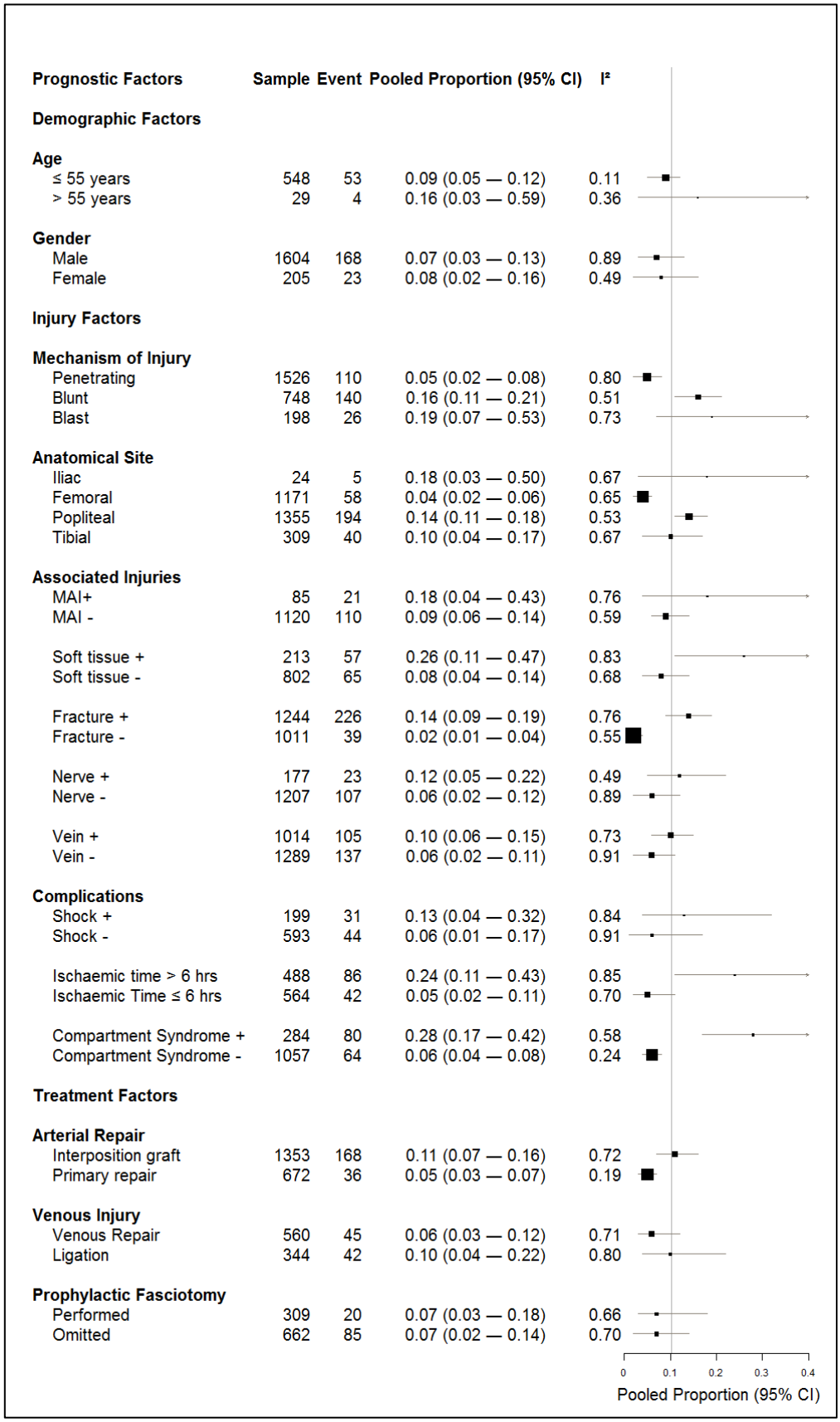


Figure 6.6: Absolute risk (pooled proportion) of secondary amputation according to identified demographic, injury, and treatment prognostic factors.

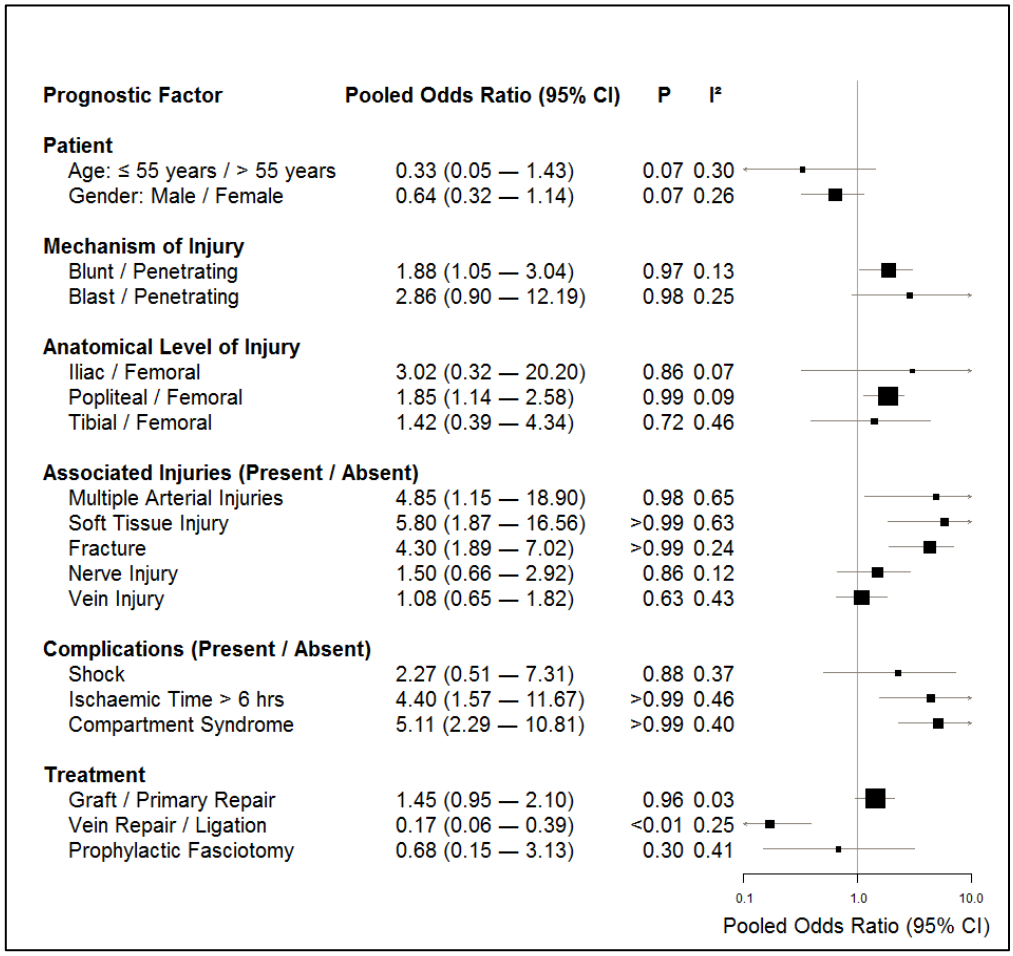


Figure 6.7: Relative risk (pooled Odds Ratio) of secondary amputation for identified demographic, injury, and treatment prognostic factors.

Table 6.5: Matrix showing the primary studies that provided information for analysis of each prognostic factor.

Reference	Age	Gender	Mechanism of Injury	Anatomical Site of Injury	Multiple Arterial Injury	Soft Tissue Injury	Fracture	Nerve Injury	Venous Injury	Shock	Duration of Ischaemia	Compartment Syndrome	Method of Arterial Repair	Method of Venous Repair	Prophylactic Faciotomy
Pourzand et al. (2010)	-	-	X	X	-	X	X	-	X	X	X	-	-	X	-
Fox et al. (2010)	-	X	X	X	-	X	X	-	X	X	X	-	X	X	-
Barros D'Sa et al. (2006)	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-
Subasi et al. (2001)	-	X	X	X	-	X	X	X	X	-	X	X	X	X	-
Nikoli et al. (2002)	-	-	X	X	X	-	X	-	-	-	-	-	-	-	-
Jie et al. (2007)	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-
Patterson et al. (2007)	-	-	X	X	-	X	X	X	-	-	X	-	-	-	-
Rozycki et al. (2003)	-	-	X	X	-	-	X	-	X	-	-	-	-	X	-
Sagraves et al. (2003)	-	-	X	X	X	-	-	-	-	-	-	-	X	-	-
Gupta et al. (2001)	X	X	X	X	X	X	X	-	X	X	X	X	X	X	X
Burkhardt et al. (2010)	X	-	X	X	-	-	-	-	-	-	-	-	X	-	-
Subramanian et al. (2008)	-	X	X	X	-	-	-	-	X	-	-	-	-	-	-
Yahya et al. (2005)	-	-	X	X	X	X	-	-	-	-	-	-	X	-	X
Simmons et al. (2012)	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-
Nair et al. (2000)	-	-	X	X	X	-	X	X	X	X	X	X	X	X	-
Nicandri et al. (2010)	-	-	X	X	X	X	X	-	-	-	X	-	X	-	-
Scott and Hirshberg (2004)	-	-	X	X	X	-	-	-	-	-	-	-	X	-	-
Klineberg et al. (2004)	-	-	X	X	X	-	X	-	-	-	-	-	X	-	X
Hafez et al. (2001)	-	X	X	X	X	-	X	X	X	-	-	X	X	X	X
Callcut et al. (2009)	-	X	X	X	-	X	-	X	X	-	-	-	-	-	-
Mills et al. (2004)	X	-	X	X	X	X	X	-	-	-	X	-	X	-	-
Moini et al. (2007)	-	-	X	X	-	-	-	-	-	-	X	-	X	-	X
Guerrero et al. (2002)	-	-	X	X	-	X	X	-	-	-	-	X	X	-	-
Davidovic et al. (2005)	X	X	X	X	-	-	X	-	X	-	X	-	X	X	-
Kuralay et al. (2002)	X	-	-	X	-	X	X	-	X	-	-	-	-	X	-
Soni et al. (2012)	X	X	X	X	X	X	X	-	-	-	X	-	X	-	X
Topal et al. (2010)	-	X	X	X	X	X	X	X	X	-	-	X	X	X	X
Perkins et al. (2012)	X	X	X	X	-	-	-	-	X	X	-	-	X	X	-
Ekim et al. (2004)	X	-	X	X	-	-	X	X	X	-	-	X	X	X	X
Kohli and Singh (2008)	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-
Degiannis et al. (2007)	-	-	X	X	-	-	-	-	-	-	-	-	-	-	-

Table 6.5: Matrix showing the primary studies that provided information for analysis of each prognostic factor (continued).

Reference	Age	Gender	Mechanism of Injury	Anatomical Site of Injury	Multiple Arterial Injury	Soft Tissue Injury	Fracture	Nerve Injury	Venous Injury	Shock	Duration of Ischaemia	Compartment Syndrome	Method of Arterial Repair	Method of Venous Repair	Prophylactic Faciotomy
Fox et al. (2008b)	X	X	X	X	-	X	X	-	X	X	X	X	X	X	-
Sriussadaporn and Pak-art (2002)	X	X	X	X	X	-	X	X	X	-	X	-	X	X	X
Miranda et al. (2002)	-	-	X	X	X	X	X	-	-	-	-	-	X	-	-
Ekim and Odabasi (2010)	-	-	X	X	-	-	X	-	X	-	-	-	-	X	-
Burg et al. (2009)	-	-	X	X	-	-	X	X	-	-	-	-	-	-	-
Woodward et al. (2008)	-	-	X	X	-	-	-	-	X	-	X	-	-	-	X
Zhu et al. (2010)	X	X	X	X	-	-	X	-	X	-	-	-	X	X	X
Kurtoglu et al. (2007)	-	X	X	X	-	-	X	-	X	-	-	X	X	X	X
Dar et al. (2003)	-	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Parmaksizoglu et al. (2010)	X	X	X	X	-	X	X	X	X	-	-	-	X	X	-
McHenry et al. (2002)	-	-	X	-	X	X	X	-	-	-	X	-	-	-	-
Makitie et al. (2006)	-	X	X	X	X	-	X	-	X	X	-	-	-	-	-
Liu et al. (2010)	-	-	X	X	-	-	X	-	-	-	-	-	X	-	-
Asensio et al. (2006)	-	X	X	X	-	-	X	X	X	X	-	-	X	X	-
Total number of articles:	12	18	41	41	17	18	32	12	24	9	16	10	28	21	12

X: study information was used in prognostic factor analysis.

6.5 Discussion

Key findings

This study provides the first comprehensive analysis of the most widely appreciated prognostic factors for amputation following LEVT. Approximately one in ten limbs that undergo vascular repair will require amputation, the rate of which varies depending on specific patient and injury characteristics. Factors associated with a substantial increase in amputation include MOI, site of arterial injury, multiple level arterial injuries, associated fracture or major soft tissue injury, ischaemic time, development of compartment syndrome, and the surgical method of vascular repair. By comparison, demographic factors, such as older age and female gender, and admission shock are associated with a smaller increase in risk, while additional venous or nerve injuries are not associated with an important increase in secondary amputation. This improved understanding of LEVT prognosis will facilitate informed decision-making and allow more accurate communication of risk with colleagues, patients and family.

Comparison to existing literature

Current understanding of prognostic factors for amputation is weak, despite being an integral component of surgical decision-making in limb-threatening injuries. This is reflected in the conflicting conclusions of published literature and the poor performance of prognostic models comprising these factors (Bonanni et al., 1993, Bosse et al., 2001, Durham et al., 1996). There may be a number of reasons for this poor performance. Firstly, the weak evidence on which many traditional prognostic factors are based - the majority were derived from small, retrospective, single-centre observational studies or expert opinion (Gregory et al., 1985, Howe et al., 1987, Johansen et al., 1990, Russell et al., 1991, McNamara et al., 1994). Secondly, it is assumed that the same prognostic factors apply to both primary and secondary amputation (ACS, 2005). This assumption is

not supported by evidence (de Mestral et al., 2013, MacKenzie and Bosse, 2006). For example, admission shock is a strong prognostic factor for primary amputation but is only weakly associated with secondary amputation (de Mestral et al., 2013, MacKenzie and Bosse, 2006). Finally, the relative strength of the relationship between each factor and amputation may be inadequately understood. As a result, many of the available amputation scores and guidelines imply an equal weighting of constituent factors (Russell et al., 1991, Howe et al., 1987, McNamara et al., 1994, Johansen et al., 1990, ACS, 2005). This generalisation overstates the importance of some factors while underestimating the impact of others (MacKenzie et al., 2002).

Explanation of findings

Damage to limb tissues may be a direct consequence of energy transfer during injury or through the effects of ischaemic necrosis. The level and extent of this tissue damage is directly related to outcome (MacKenzie et al., 2000, MacKenzie et al., 2002, Kauvar et al., 2011, de Mestral et al., 2013, Mullenix et al., 2006, Tan et al., 2011). A number of injury characteristics are markers of these processes and have been used as prognostic factors (ACS, 2005, Scalea et al., 2012). The results of this meta-analysis demonstrate the wide variation in prognostic significance of these characteristics, ranging from a greater than five-fold increase in secondary amputation for LEVT associated with severe soft tissue injury or complicated by compartment syndrome, to a relatively weak relationship between additional venous or nerve injuries and amputation.

The method of vascular repair is determined by the degree of vascular injury and therefore should also bear prognostic significance. Surprisingly, none of the individual studies in our review identified a significant relationship between the method of arterial repair and secondary amputation. However, meta-analysis of their results shows a 50 percent higher risk of amputation for arterial injuries that require an interposition graft compared to those that can be primarily repaired. Similarly, the management of a venous

injury is strongly associated with outcome. Venous ligation is frequently used as a damage control procedure in patients with complex venous injuries, especially those that are physiologically compromised (Aucar and Hirshberg, 1997). This procedure seems to be a more effective marker of the extent of injury, and therefore prognosis, than simply the presence or absence of a venous injury.

Demographic characteristics, such as age and gender, are recognised prognostic factors for functional and psychological outcomes after major injuries, including severe lower extremity trauma (MacKenzie and Bosse, 2006, Holbrook et al., 2001). Although age was traditionally believed to be an important prognostic factor (ACS, 2005, Gregory et al., 1985, Johansen et al., 1990, McNamara et al., 1994), neither age nor gender has been shown to be prognostic of amputation in large observational studies (de Mestral et al., 2013, MacKenzie et al., 2000, Mullenix et al., 2006). Furthermore, none of the studies included in this review identified an association between demographic factors and secondary amputation. Shackford et al. (2013), however, observed a significant relationship between demographic factors and secondary amputation in extremity vascular injuries requiring interposition grafts. This meta-analysis shows a higher amputation in those older than 55 years but should be interpreted with caution, as the pooled sample of older patients is small (29 patients) with only four undergoing secondary amputation. Surprisingly, meta-analysis also shows a small but significant increase in secondary amputation in females. A possible explanation may be the confounding effect of injury characteristics and we are investigating this relationship further. Overall, demographic factors are comparatively weak predictors of secondary amputation and should not be relied upon in amputation decisions.

Implications of findings

Few of the identified prognostic factors have the potential to be modified. However, those that can be modified provide substantial opportunities for improved outcome. The

duration of limb ischaemia, development of compartment syndrome, and presence of haemorrhagic shock are key modifiable determinants of outcome, and trauma systems should have strategies in place to promptly recognise and manage these emergencies (Percival and Rasmussen, 2012, Brohi et al., 2011). Effective interventions include the appropriate use of tourniquets (Beekley et al., 2008, Kragh et al., 2009), temporary vascular shunts (Rasmussen et al., 2006b, Gifford et al., 2009, Glass et al., 2009), fasciotomies (Percival and Rasmussen, 2012, Nanchahal J, 2009), and damage control resuscitation (Fox et al., 2008a) ; and the efficient triage of patients with limb-threatening injuries to specialist centres with the requisite expertise, equipment and resources (Nanchahal J, 2009, Mackenzie et al., 2008). In addition, the surgical management of concomitant venous injuries may have an important impact on limb outcome. Repair of deep venous injuries proximal to the trifurcation is recommended (Nanchahal J, 2009, Kuralay et al., 2002).

6.6 Strengths and limitations

Strengths

This analysis is based on a large sample of patients with limb-threatening vascular injuries from a wide spectrum of geographical and economic locations. The findings advance the understanding of prognostic factors for secondary amputation and will be applicable in a wide variety of settings. This knowledge may also provide the opportunity to develop improved decision-support tools for severe lower limb injuries. Furthermore, the Bayesian approach provides robust conclusions and overcomes many of the limitations of conventional meta-analysis methods for observational studies.

Analyses of methodological differences between studies did not show any significant risk of bias. A small difference in effect is observed when comparing the method of data collection (retrospective versus prospective). The majority of prospective studies only

included patients with vascular injuries resulting from knee dislocations. The relatively low burden of tissue damage in these injuries provides an explanation for the lower amputation rate observed. Additionally, studies with a short duration of follow-up may under-report the true secondary amputation rate, as a small proportion of secondary amputations are performed as a delayed procedure months to years after injury (Bosse et al., 2002, Krueger et al., 2012). Similarly, studies with lower methodological quality may also under-report secondary amputation rates. These two factors may have influenced results in this study, albeit not significantly.

Limitations

This study has a number of limitations. As is the case with all meta-analyses, our results are dependant on the content and quality of reporting in the included studies. Categorisation of continuous prognostic factors in the primary studies, and in our analyses, may have reduced prognostic information and power (Altman and Royston, 2006). Furthermore, observational studies are prone to confounding and variation between studies may not be random. Indeed, we found large heterogeneity between included studies. Both clinical and methodological reasons for this heterogeneity were explored and analyses were performed using models that account for heterogeneity. The majority of heterogeneity was clinical, related to study population differences. This should be considered when interpreting the overall secondary amputation risk of patients with LEVT. We analysed the unadjusted association between each prognostic factor and secondary amputation. Clearly, many of the identified prognostic factors are related and future studies are needed to investigate their confounding influences. Finally, it is possible that other important prognostic factors for secondary amputation exist that were not identified by the search.

CHAPTER SEVEN

Development and Validation of a Prognostic Model for Limb Viability

7.1 Introduction

Assessing the risks associated with surgical intervention, or no intervention, is a cornerstone of informed decision-making (Dickson and Chong, 2009). Severe lower limb injuries, especially those that involve vascular trauma, pose a number of risks to the patient, including a risk to their life and to their limbs viability and future function. The degree of each risk is variable and influenced by a number of factors, the most important being the characteristics of the injury, the treatment provided, and the time taken to intervene. Deciding the treatment strategy most likely to achieve the best outcome is complex. Good judgement requires the ability to estimate the risks associated with an individual injury, and estimate the impact different treatment strategies may have on these risks. In *Chapter Four*, a diagnostic model for Trauma Induced Coagulopathy (TIC) was developed. TIC is a key determinant of the need for life-saving intervention, and an accurate estimate of the risk of TIC is critical during initial therapeutic decision-making. TIC, however, is not the only risk that needs to be considered when managing a patient with a severe lower limb injury. The risk to limb viability also requires careful consideration. In this chapter, a model that can quantify the risk to limb viability is developed.

Damage to limb tissues may be a direct consequence of energy transfer during injury or secondary to ischaemic necrosis due to prolonged disruption of the tissues blood supply. The level and extent of this tissue damage determines the limb's viability and directly influences therapeutic decisions (MacKenzie et al., 2002, de Mestral et al., 2013, Nanchahal J, 2009). Ideally, surgical management would include rapid reperfusion of the limb to limit ischaemic damage, followed by reconstruction of the injured tissues to salvage the limb's function. However, in some situations, attempts at limb reperfusion or reconstruction may be harmful, and early amputation may achieve the best overall

outcome (Bondurant et al., 1988, Percival and Rasmussen, 2012). Limb viability is one of the most important factors that influence these surgical decisions (Percival and Rasmussen, 2012, Glass et al., 2009). Indeed, a non-viable limb was the principal reason for half of all amputations following lower extremity vascular trauma during the recent wars in Iraq and Afghanistan (*Chapter Three*).

Estimating the risk to limb viability can be challenging. With improved trauma systems, only a small proportion of casualties with limb-threatening injuries have delayed access to care, and present with clearly non-viable limbs (Rasmussen et al., 2006a, White et al., 2011a). In these cases, decision-making is straightforward, as there are no alternatives to amputation. However, in the majority of cases, the risk to limb viability is unclear at the time of initial wound assessment. This uncertainty makes decision-making difficult. A means to accurately estimate the predicted outcome of limb reperfusion and projected limb viability would improve individual risk assessment and support informed therapeutic decisions.

7.2 Aims and objectives

The aim of this study was to develop a prognostic model for limb viability, and validate the model's performance in a cohort of patients with severe lower limb trauma.

The *first* objective was to develop an evidence-based Bayesian Network for limb viability that can be used to predict the risk of a non-viable limb.

The *second* was to assess the predictive performance of the model in a cohort of severe lower limb injuries.

Third, was to compare the performance of the prognostic model against the performance of the Mangled Extremity Severity Score (MESS), at predicting amputations because of a non-viable limb.

7.3 Methods

7.3.1 Study design and Participants

This study describes the development and validation of a prognostic model for limb viability following severe lower limb trauma that includes a vascular injury. The prognostic model was developed using Bayesian networks. The methodology combined knowledge and data (Yet et al., 2014c) from a systematic review and meta-analysis (*Chapter Six*) and a large cohort study, the Global War On Terror Vascular Injury Initiative (GWOT-VII). GWOT-VII was reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and informed consent was obtained for all participants. This study represents a collaboration between the Centre for Trauma Sciences, and the School of Electronic Engineering and Computer Science, at Queen Mary, University of London; the United Kingdom's Academic Department of Military Surgery & Trauma (ADMST); and the United States Army Institute of Surgical Research (USAISR).

7.3.2 Sources of information:

Systematic Review and Meta-Analysis

Information from a systematic review of the contemporary literature on prognostic factors for amputation following lower limb vascular trauma (*Chapter Six)* was used to inform model development. The review was performed according to PRISMA guidelines and the study protocol was prospectively published on the PROSPERO register (CRD42012002720). Relevant publications were identified by an electronic search of the MEDLINE, EMBASE, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases between January 2000 and July 2012. Additional publications were

identified from the reference lists of included studies. Studies that described the outcome of adults undergoing surgical repair of lower extremity vascular trauma were eligible for inclusion. Patient, injury, and treatment factors associated with limb amputation were identified from the included studies. Bayesian meta-analysis was used to calculate an absolute (pooled proportion) and relative (pooled Odds Ratio) measure of the amputation risk associated with each of the identified prognostic factors.

Cohort study

GWOT-VII is a cohort study that maintains prospective follow-up of US military servicemen who sustained extremity vascular trauma while serving in the wars in Iraq and Afghanistan (Stannard et al., 2012). Cases are identified from the Joint Theatre Trauma Registry (JTTR), which is a comprehensive database of all injured casualties treated at US Military treatment facilities. Both registries are held and maintained by the United States Army Institute of Surgical Research (USAISR) at Fort Sam Houston, Texas.

Potential participants for this study were identified from the GWOT-VII database. US servicemen who sustained a major lower extremity injury involving at least one named lower extremity artery, distal to the aortic bifurcation, between 01 March 2003 and 01 February 2012, were eligible for inclusion. Exclusion criteria were: complete traumatic limb amputation; primary resuscitative (Damage Control) limb amputation; injuries that underwent amputation because insufficient tissue remained for reconstruction; isolated Profunda Femoris injuries; and iatrogenic vascular injuries. Cases where the reason for limb amputation was not clearly documented were also excluded. The model is developed to predicting the risk of a non-viable limb. Primary resuscitative amputations were excluded as the viability of the limb, had salvage been pursued, is unknown. Similarly, amputations performed because insufficient tissue remained for reconstruction were also excluded, as the reason for amputation is poor predicted function, and limb viability if salvage was pursued is unknown. Isolated Profunda Femoris artery trauma was excluded,

as these injuries have minimal affect on limb viability when the femoral-popliteal-tibial axis is patent. Furthermore, Profunda Femoris trauma was not identified as a risk factor for amputation in the systematic review. Finally, iatrogenic vascular injuries were excluded as they fall outside of the intended scope of the model.

7.3.3 Data collection

Data on selected patient, injury, and acute management variables were extracted from the GWOT-VII database and the JTTR. This is supplemented and corroborated with additional information from the Armed Forces electronic medical records, patient questionnaires and direct patient contact. Data accuracy and quality is assured and maintained by specially trained research nurses. Injury severity was classified by trained personnel according to the Injury Severity Score (ISS) (Baker et al., 1974) and Mangled Extremity Severity Score (MESS) (Johansen et al., 1990). Outcome data, in terms of limb viability and indications for amputation, were obtained from operative records, multi-discipline meeting records, clinic letters, patient questionnaires, and patient interviews. All patients were followed-up until 01 February 2013, one year after the end of the study period.

7.3.4 Outcome

The primary outcome was limb viability. Viability was defined as limb tissue with the capacity to survive and live successfully (OED, 2015). Each injured limb included in the study was classified as either viable or non-viable. Limbs were classified as viable if they did not undergo amputation during the study period; underwent an elected secondary amputation for functional limitations, chronic pain, or chronic osteomyelitis; or were successfully reconstructed and then suffered a second traumatic injury or iatrogenic insult that resulted in amputation. Limbs were classified as non-viable if they underwent amputation and the documented reason for amputation was non-viable limb tissue.

7.3.5 Model development

The prognostic model was developed using Bayesian Networks (BNs), a powerful technology that permits multiple sources of information to be combined and used to calculate predictions (Fenton and Neil, 2012b). BNs consist of two parts: a network structure that graphically describes the models' variables and their relations, and a set of parameters that captures the strength of the relationships between variables. The BN was developed using a methodology that allows the combination of existing knowledge and data. The method follows a step-wise approach that is described below. A detailed explanation of the methodology has been published (Yet et al., 2014c).

Step 1) Predictor Selection

Variables included in the model were selected using clinical knowledge. By definition, all non-viable limbs will ultimately require amputation, however not all amputations are performed because of a non-viable limb. Prognostic factors for amputation following lower extremity vascular trauma were identified by a systematic literature review (*Chapter Six*). The mechanistic relationship between each of the identified prognostic factors and limb viability was assessed, and variables that were mechanistically related to limb viability were included in the BN model. To avoid over-fitting, data from the cohort study was not used to select predictors.

Step 2) Predictor states

The possible states that each predictor can take were also defined using clinical knowledge. The systematic review identified fifteen categorical variables. However, four of these variables are continuous variables (age, degree of soft tissue injury, degree of shock, and duration of ischaemia) that had been dichotomised by the constituent studies included in the review. Dichotomising continuous variables may be convenient for descriptive purposes but significantly reduces the predictive power of the variable (Altman and Royston, 2006). To overcome this limitation, dichotomised predictors

included in the BN were modelled as ordinal variables with more than two clinically relevant categories. The thresholds for these categories were informed by clinical knowledge. The remaining predictors were modelled using the states identified by the systematic review. To avoid over-fitting, data from the cohort study was not used to define the predictor states.

Step 3) Network Structure

The network structure is a graphical representation of the clinical problem. It takes the form of a directed acyclical graph that consists of nodes and edges. Each node represents a variable and the directed edges represent the relationships between the variables. Developing a network structure that represents the causal mechanisms and clinical understanding of a problem is important (Fenton and Neil, 2012a). Such models have improved face validity, clinical credibility, avoid over-fitting, and enable generality to populations other than the population the model was developed from. These are essential properties of clinically useful prognostic models (Wyatt and Altman, 1995). Data-driven approaches, that ignore clinical knowledge, may produce models that contradict common sense and clinical understanding, and fail to satisfy many of the properties of a clinically useful tool.

The model was built in fragments corresponding to the level of arterial injury. Clinical knowledge was used to define the mechanistic relations between predictor variables and limb viability. Where required, latent variables were introduced to model important intermediate mechanistic steps. In this way, a structure that reflects the current clinical understanding of factors that influence limb viability was developed. Identical fragments were then combined to produce a mathematically efficient model. To avoid over-fitting, data-driven approaches were not used to inform the models structure.

Step 4) Parameter learning

A set of parameters, that quantifies the relationship between a variable and those variables related to it, was defined for each node. These parameters are probability values assigned to each of the possible states of the variable that the node represents. The parameters of a given node are conditioned on the possible states of its parent nodes. For nodes without parents, the parameter is estimated from the prior probability of the respective state occurring in the population of interest. For each node, a Node Probability Table (NPT) was constructed that contains a set of all possible probability values the node can take given its relations.

Parameters were learned from clinical knowledge and data. The meta-analysis in *Chapter Six* provides a pooled estimate of probabilities and odds ratios for univariate relationships. These were used to model the respective nodes in the Bayesian network with a single parent. The meta-analysis results, however, cannot be directly used for nodes with multiple parents or for relationships with intermediate nodes. Parameters for the remaining nodes were learned by combining the results of the meta-analysis with data from the cohort study using the method described by Yet et al. (2014c).

Step 5) Cross Validation

The predictive performance of the model was tested using ten-fold cross validation (Kohavi, 1995). In this approach, the development cohort is randomly divided into ten equal size samples. Nine samples are used to train the model and the performance is then tested on the remaining sample. The process is repeated ten-fold, with each sample used once as test data. The results are then combined to calculate a performance estimate. Using this method, the model is trained and internally validated on two statistically independent cohorts containing all of the development data. Ten-fold cross validation is the recommended method of estimating the predictive performance of a model in a new population (Kohavi, 1995). It has a number of advantages over other methods such as

holdout and bootstrapping, including less bias, less variance, and a low risk of over-fitting.

7.3.6 Performance

The model's predictive performance was assessed using multiple measures of discrimination, calibration and accuracy. Discrimination was measured using the Area Under the Receiver Operating Characteristic curve (AUROC) (Swets, 1988), sensitivity, specificity, and the Diagnostic Odds Ratio (DOR) (Glas et al., 2003). The AUROC has a value between 0.5 (no discriminatory ability) and 1.0 (perfect model). Models with an AUROC greater than 0.9 may be regarded as having excellent performance, whereas 0.7 to 0.9 indicates moderate performance, and 0.5 to 0.7 poor performance. The DOR is the ratio of the odds of a positive prediction among those with the condition relative to the odds of a positive prediction among those without the condition. The value of DOR ranges from 0 to infinity, with higher values indicating better discriminatory performance. As a general rule, a potentially useful tool will have a DOR above 25, while a DOR of less than 25 indicates an unhelpful tool (Jaeschke et al., 1994, Deeks, 2001). Calibration measures whether the predicted probability agrees with that observed. Calibration was evaluated using the Hosmer-Lemeshow (HL) test statistic (Hosmer and Lemesbow, 1980) and by visual assessment of the predicted and observed frequency of coagulopathy in 10 equal groups stratified by risk. A low HL p-value indicates poor calibration. Accuracy combines features of discrimination and calibration to measure how close, on average, predicted outcomes are to actual outcomes. Accuracy was evaluated with the Brier Score (BS) (Brier, 1950) and the Brier Skill Score (BSS) (Weigel et al., 2007). The BS has a value between 0 (perfect model) and 1 (worst possible model) and the BSS has a range from - ∞ to 1, where a negative value indicates a worse prediction than the average probability and 1 indicates a perfect model.

7.3.7 Sensitivity analyses

The impact that each predictor variable has on the models probability calculations was assessed using one-way sensitivity analyses. The results were plotted on a tornado graph. This enables a visual comparison of the relative impact each predictor variable has in the final model.

The study population includes patients that underwent both primary and secondary amputations. Primary amputations were performed for clearly non-viable injuries. Including primary amputations in the validation population may exaggerate the performance of the model, as these cases are likely to have high predictions that correlate with their amputation outcome. Furthermore, the performance of the model in patients where limb viability is unclear has greater clinical value, as the results have the potential to support early decisions that avoid potentially harmful salvage attempts. The performance of the model on the whole study population was therefore compared to its performance on the study population with all primary amputations excluded.

7.3.8 Comparison to the Mangled Extremity Severity Score (MESS)

Finally, the predictive performance of the Bayesian Network model was compared to that of the MESS. MESS is a well-established score designed to predict the risk of amputation, defined as a non-viable limb rather than a dysfunctional limb, in patients with lower extremity vascular trauma (Johansen et al., 1990). Trained personnel, independent of this study and blind to the structure and results of the Bayesian Network, calculated all MESS scores at the time of initial wound evaluation.

7.3.9 Statistical analyses

Statistical analyses were performed using GraphPad PRISM v6 (GraphPad, La Jolla, CA, USA) or SPSS v20 (SPSS, Chicago, Il, USA). The Bayesian Network model was developed with, and is powered by, AgenaRisk software (Agena, London, UK). Normal-quartile plots were used to test for normality. Unless otherwise specified, categorical data

are reported as frequency with percent and numerical data as median with Inter Quartile Range (IQR). Where appropriate, the chi- square ($\chi 2$) or Fisher's exact test were used to compare categorical data and the Mann-Whitney U-test was used to compare numerical data. The area under ROC curves was calculated and compared using the method described by Hanley and McNeil (Hanley and McNeil, 1982). The area under correlated ROC curves was compared using a non-parametric method that accounts for the paired test design (DeLong et al., 1988). Area under ROC curves and DOR are reported with their corresponding 95 percent confidence intervals (CI). Statistical significance was set as a two-tailed P-value of <0.05.

7.4 Results

7.4.1 Study population

Between 01 March 2003 and 01 February 2012, 576 US soldiers sustained lower extremity vascular injuries in 601 limbs, and were included in the GWOT-VII registry. Ninety-one injured limbs met the clinical exclusion criteria for this study: traumatic amputation (19), primary resuscitative amputation (19), amputation because insufficient tissue remained for reconstruction (23), isolated Profunda Femoris Artery injury (27), and iatrogenic vascular injury (3). Two cases were excluded because the reasons for amputation were unclear. Data from the remaining 508 injured limbs, in 487 soldiers, were used to develop and validate the model. The median age of included soldiers was 23 (range: 18 – 54) years, and 339 limbs (66.7 percent) sustained a blast mechanism of injury. The median Injury Severity Score was 14 (10 – 21) and the median Mangled Extremity Severity Score for injured limbs was 6 (5 – 7). Baseline characteristics of the study population are shown in Table 7. 1.

7.4.2 Outcome

All 508 included limbs sustained injuries that threatened limb viability. Fourteen limbs (2.8 percent) were assessed as clearly non-viable at initial presentation and were treated with primary amputation. The remaining 494 limbs underwent surgery to reperfuse the limb. Of these, 444 limbs (89.9 percent) remained viable and 50 limbs (10.1 percent) became non-viable. All 50 non-viable limbs underwent secondary amputation. These procedures were performed between one day and 59 days after injury.

In addition, 31 viable limbs (7.0 percent) also underwent amputation. The reasons for, and timing of, viable limb amputations were: 29 elected amputations for functional limitations, chronic pain, or chronic osteomyelitis (performed between 49 and 922 days after injury); one iatrogenic injury (11 days after injury); and one case resulting from

complications of a second traumatic injury (1848 days after the original injury). Baseline characteristics of viable and non-viable limbs are shown in table 7.1.

Table 7.1: Baseline characteristics of 508 injured limbs according to outcome.

Characteristic	Missing Data (%)	Viable (N=444)	Non-viable (N=64)	P-value
Age – years (range)[a]	<1	23 (18 - 54)	23 (19 - 46)	0.599
Mechanism of Injury - Blast	0	288 (64.9)	51 (79.7)	0.023
Injury Severity:				
Injury Severity Score[a]	5.3	14 (10 – 18)	21 (16 – 29)	< 0.0001
Mangled Extremity Severity Score	5.7	6 (5 – 6)	7 (6 – 7)	< 0.0001
Arterial injury:				
Iliac Artery	0	13 (2.9)	3 (4.7)	0.439
Femoral Artery	0	142 (32.0)	25 (39.1)	0.259
Popliteal Artery	0	89 (20.0)	21 (32.8)	0.034
Tibial Arteries	0	200 (45.1)	15 (23.4)	0.001
Multiple Arterial Injuries	0	16 (3.6)	13 (20.3)	<0.0001
Associated Injuries:				
Soft tissue injury - Severe	23.4	48 (14.6)	48 (78.7)	< 0.0001
Fracture	3.5	214 (50.2)	56 (87.5)	< 0.0001
Venous injury	0	179 (40.3)	34 (43.1)	0.058
Nerve injury	13.2	130 (34.0)	24 (40.7)	0.379
Complications:				
Shock - uncompensated	2.0	78 (17.8)	41 (67.2)	< 0.0001
Duration of ischaemia > 6 hours	48.2	1 (0.4)	17 (47.2)	< 0.0001
Compartment Syndrome	0	29 (6.5)	4 (6.3)	1.000
Treatment factors:				
Primary repair	3.1	77 (17.9)	7 (11.1)	0.212
Interposition graft	3.1	219 (51.0)	40 (63.5)	0.079
Ligation	3.1	133 (31.3)	14 (22.2)	0.185

Categorical data presented as number (percent) and numerical data presented as median (IQR)

[a] Refers to 487 soldiers with limb injuries.

7.4.3 Model development

Predictors

The systematic review (*Chapter Six*) identified 45 relevant studies that described the outcome of 3187 lower extremity vascular injuries. From these studies, 15 potential prognostic factors for amputation were identified. Nine of these predictors were considered mechanistically related to limb viability and included in the model (Table 7.2). The six factors not included in the model were age, gender, associated nerve injury, associated venous injury and method of repair, and prophylactic fasciotomy.

The majority of predictors were modelled using the states identified in the systematic review. Four variables (degree of soft tissue injury, degree of shock, duration of ischaemia, and Tibial artery injury) were modelled in more detail than the dichotomised states identified in the systematic review. Definitions of the possible states of each predictor included in the model are presented in table 7.2.

Network Structure

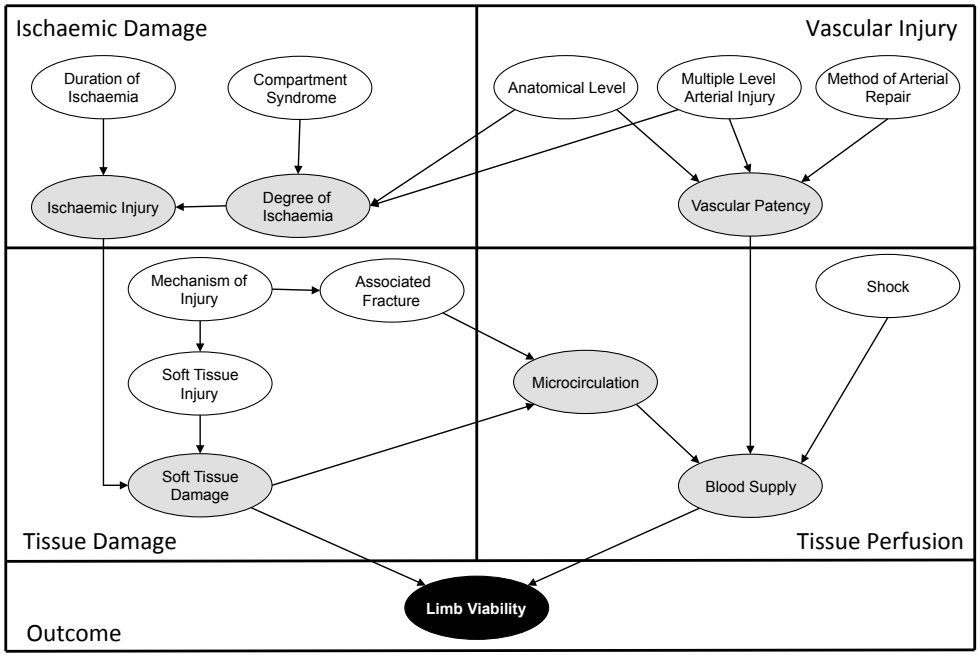
The network structure of the model captures the relations between predictor variables, latent variables, and outcome (Figure 7.1 A and B). The final model's structure is composed of two fragments. One fragment relates to injuries that involve arteries above the popliteal trifurcation, and the other relates to injuries involving arteries below the trifurcation. Each fragment has four components. These components correspond to key mechanistic determinants of limb viability: 1) degree of ischaemic damage, 2) degree of tissue damage, 3) adequacy of tissue perfusion, and 4) characteristics of the vascular injury.

Table 7.2: Definitions of predictor variables in the Bayesian Network model.

Predictor Variable	Type of Node	Definition
Mechanism of Injury	Labelled	*Blast / Blunt / Penetrating*
Arterial Injury:		
Anatomical Level	Labelled	Level of arterial injury divided into four anatomical zones: *Iliac* (includes common and external iliac arteries), *Femoral* (includes common and superficial femoral arteries), *Popliteal*, and *Tibial* (includes peroneal, anterior tibial and posterior tibial).
Number of Tibial Arteries Injured	Numeric	Number of Tibial arteries injured, discrete whole number between 0 and 3.
Multiple Level Arterial Injury	Boolean	Arterial injuries at more than one anatomical level: *yes / no*.
Associated Injuries:		
Soft Tissue Injury	Ranked	Degree of soft tissue injury at the same level as arterial injury.[a] *None*, *Mild* (no tissue loss), *Moderate* (< 25 percent tissue loss), *Severe* (25 – 75 percent tissue loss), *Profound* (> 75 percent tissue loss, mangled extremity)
Fracture	Boolean	Fracture or dislocation at same level as arterial injury: *yes / no*.
Complications:		
Shock	Ranked	Degree of haemorrhagic shock: *None* (SBP always > 90mmHg, ≤ 2 units blood/24 hours), *Compensated* (SBP transiently below 90mmHg, > 2 units blood/24 hours), or *Uncompensated* (SBP consistently below 90mmHg, massive blood transfusion, coagulopathy).
Duration of Ischaemia	Ordinal	1) *Less than one hour*, 2) *between one and three hours*, 3) *between three and six hours*, and 4) *greater than six hours*.
Compartment Syndrome	Boolean	*Present / Absent*
Method of Arterial Repair	Labelled	*Primary repair* (including thrombectomy, lateral repair, patch angioplasty and end-to-end anastomosis), *Interposition Graft* (including those performed with autologous vein and those with prosthetic material), *Ligation*, and *Temporary Vascular Shunt.*

[a] Degree of soft tissue injury is measured in the anatomical zone of the limb corresponding to the arterial injury: Thigh (Femoral), Knee (Popliteal), and Leg (Tibial). SBP, Systolic Blood Pressure

A) Above-Trifurcation Fragment



B) Below-Trifurcation Fragment

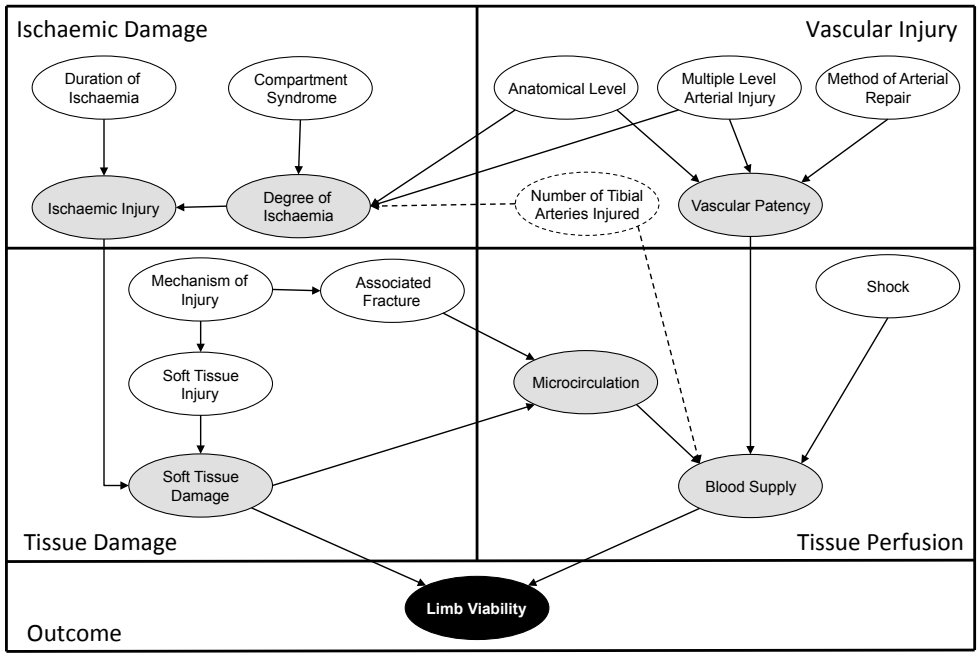


Figure 7.1: Structure of the Bayesian Network prognostic model. Predictor variables (white), latent variables (grey), and the outcome variable (black) are presented together with the directions of the relationships between variables. The model is divided into two fragments: Above-Trifurcation (**A**) and below-Trifurcation (**B**). Each fragment has four

causal components. The dashed lines represent a variable that is only present in the Below-Trifurcation fragment.

7.4.4 Performance

The model had excellent overall performance at predicting limb viability. The AUROC was 0.932 (95 percent CI: 0.898 – 0.967) (Figure 7.2). When operated at a threshold probability of 0.21, the sensitivity was 90.6 percent, specificity 85.5 percent, and DOR 56.8 (95 percent CI: 43.1 – 74.9). On visual inspection, the predicted risk of a non-viable limb calibrated well with the observed outcome (Figure 7.3); and the Hosmer-Lemeshow goodness-of-fit test result was not significant (HL statistic: 14.1; p = 0.079). Overall, the models predictions were accurate, with a Brier Score of 0.06 (95 percent CI: 0.05 – 0.07) and a Brier Skill Score of 0.39 (95 percent CI: 0.25 – 0.48). The predictive performance of the 'Above-Trifurcation' and 'Below-Trifurcation' fragments of the model were similar and are shown in Table 7.3.

7.4.5 Sensitivity analyses

All predictor variables contributed to the model's result, with the degree of soft tissue injury, degree of ischaemic tissue damage, and degree of shock having the greatest impact on predictions (Figure 7.4).

Fourteen limbs underwent primary amputation. In these cases, the median predicted probability of a non-viable limb was 0.50 (range: 0.30 – 0.74). At a threshold of 0.21, the model predicted all primary amputations. Excluding primary amputations from the validation population did not have any significant affect on the models performance. The AUROC was 0.923 (0.880 – 0.965) and at a threshold of 0.21 the sensitivity was 90.0 percent, specificity 85.5 percent, and DOR 53.1 (95 percent CI: 40.5 – 69.6).

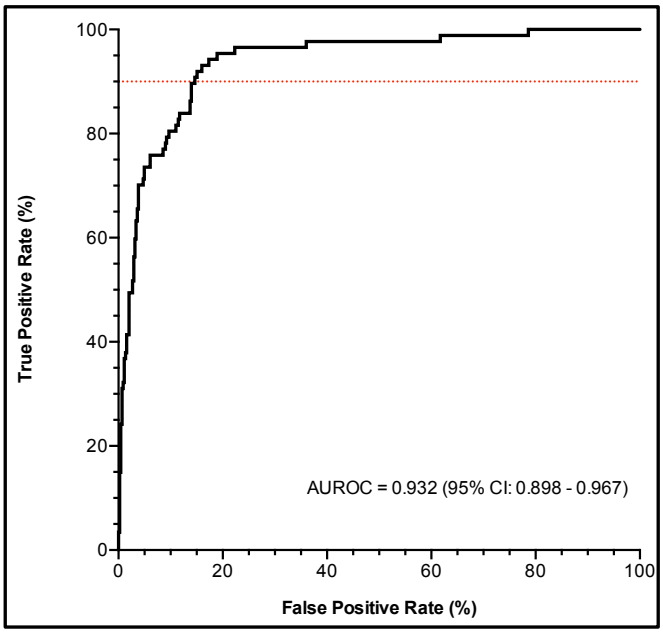


Figure 7.2: Overall accuracy of the limb viability prognostic model. Overall accuracy was assessed using Area Under the Receiver Operating Characteristic (AUROC) curve for viability predictions in a cohort of 508 severe lower limb injuries. This plots the true positive rate (sensitivity) against the false positive rate (1 – specificity). The AUROC was 0.932. At a sensitivity of 90 percent the false positive rate was 15 percent.

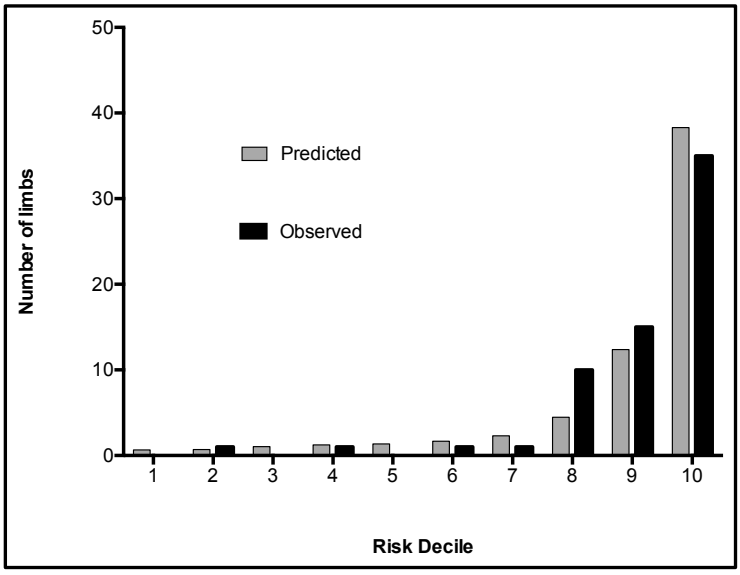
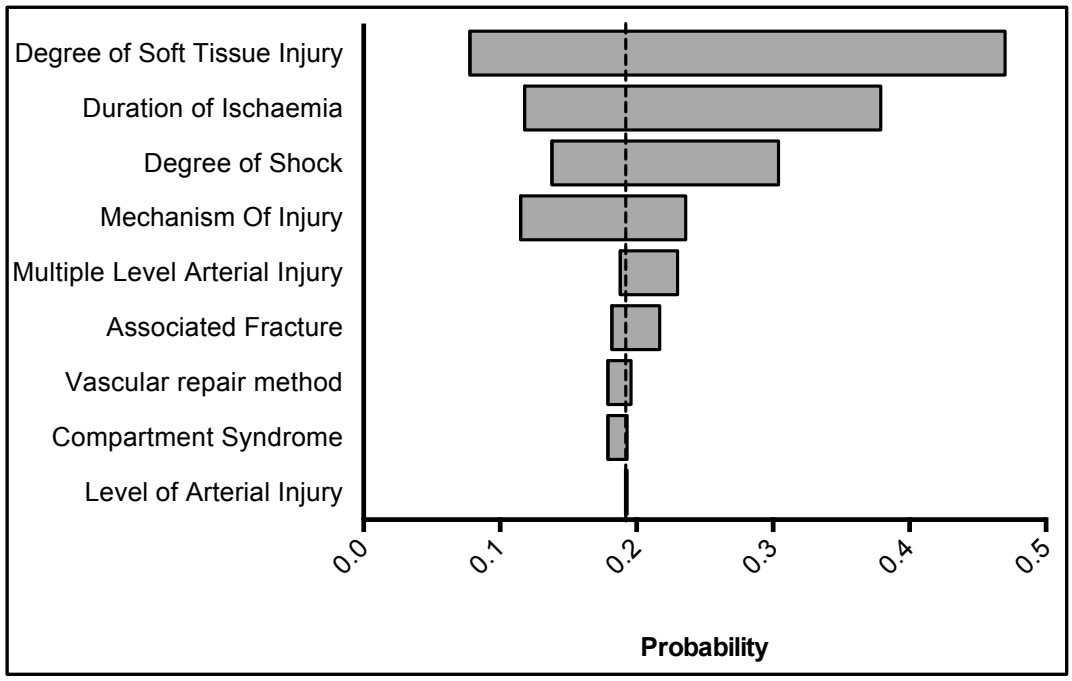


Figure 7.3: Model calibration in cohort of 508 severe lower limb injuries. The Hosmer and Lemeshow test statistic was 14.1 and there was no significant difference between the predicted and observed frequency of a non-viable limb in each risk group (p = 0.079).

A) Above-Trifurcation Fragment



B) Below-Trifurcation Fragment

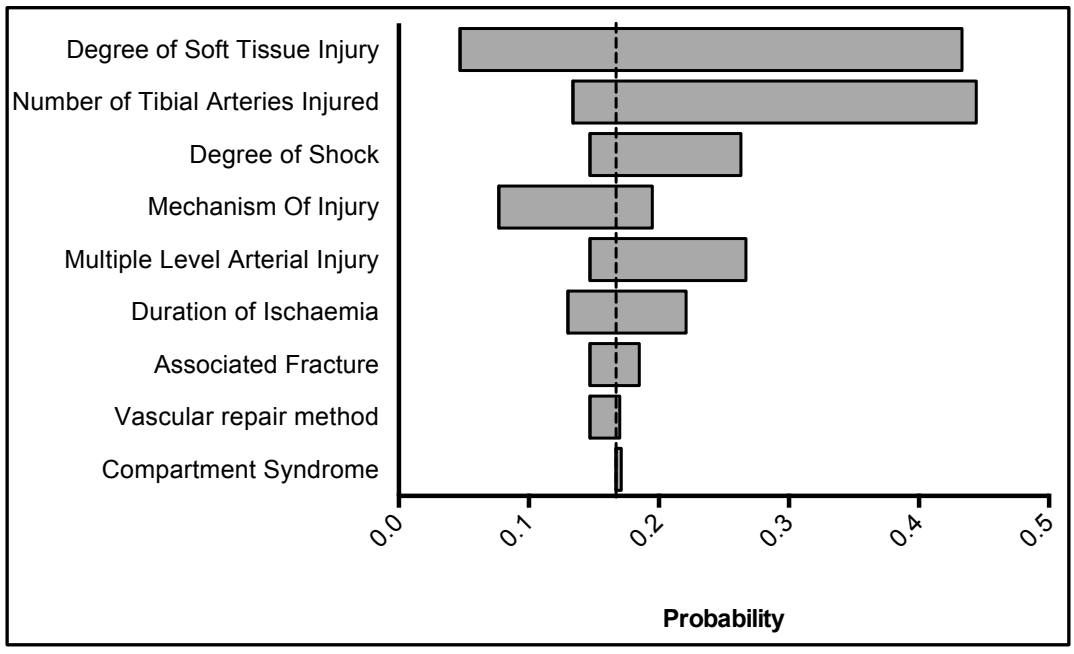


Figure 7.4: One-way sensitivity analyses of the impact individual predictor variables have on the models result. A) Impact of predictors in the Above-Trifurcation fragment, B) Impact of predictors in the Below-Trifurcation fragment. The dotted line represents the prior probability of amputation in each population.

Table 7.3: Predictive performance of the Above- and Below-Trifurcation fragments of the limb viability model.

Performance Measure	Above-Trifurcation Fragment (n=293)	Below-Trifurcation Fragment (n=215)
Discrimination:		
AUROC	0.945 (0.907 – 0.984)	0.895 (0.821 – 0.968)
Specificity (%) [a]	86.0 (80.9 – 90.1)	80.0 (73.8 – 85.3)
DOR	54.1 (41.2 – 71.0)	55.7 (41.6 – 74.6)
Calibration:		
Hosmer-Lemeshow statistic	5.1 (p = 0.745)	11.4 (p = 0.180)
Accuracy:		
Brier Score	0.06 (0.05 – 0.08)	0.05 (0.03 – 0.07)
Brier Skill Score	0.46 (0.35 – 0.57)	0.15 (-0.15 – 0.45)

Data are presented with 95 percent Confidence Intervals unless otherwise specified.

[a] Specificity calculated at 90 percent sensitivity.

AUROC, Area Under the Receiver Operator Characteristic Curve; DOR, Diagnostic Odds Ratio.

7.4.6 Comparison to the Mangled Extremity Severity Score (MESS)

Four hundred seventy nine injured limbs (94.3 percent) had a MESS score available for comparison. The median MESS was 6 (Range: 1 – 10). One hundred thirty six injured limbs (28.4 percent) had a MESS greater or equal to seven, the recommended threshold to predict the need for amputation, while 343 limbs (71.6 percent) had a MESS less than seven. Of the limbs predicted to need amputation by the MESS, 48 (35.3 percent) underwent amputation, 35 (25.7 percent) because of a non-viable limb and 13 (9.6 percent) for other indications. Of the limbs predicted as salvageable by MESS, 41 (12.0 percent) underwent amputation, 23 (6.7 percent) because of a non-viable limb and 18 (5.2 percent) for other indications.

The MESS had only a moderate ability to predict limb viability. The AUROC was 0.723 (95 percent CI: 0.656 – 0.790) and at a threshold of seven the sensitivity was 60.3 percent, specificity 76.0 percent, and DOR 4.8.

The MESS had significantly worse ability to predict the need for amputation for any indication. The AUROC was 0.540 (95 percent CI: 0.444 – 0.635) and at a threshold of seven the sensitivity was 53.9 percent, specificity 77.4 percent, and DOR 3.9.

The BN prognostic model had significantly better performance than MESS at predicting limb viability (AUROC 0.932 (0.898 – 0.967) versus 0.723 (0.656 – 0.790); P < 0.0001)(Figure 7.5). A comparison of performance measures of the BN prognostic model and the MESS are shown in Table 7.4.

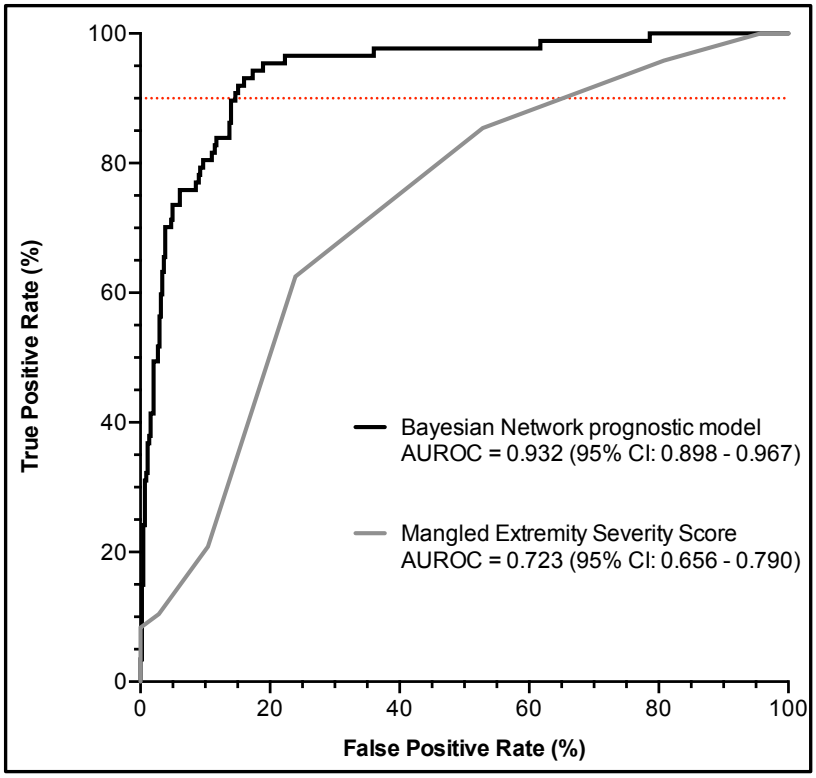


Figure 7.5: Comparison of the Area Under the Receiver Operator Characteristic (AUROC) curve for predicting amputations performed because of a non-viable limb using a Bayesian Network prognostic model and the Mangled Extremity Severity Score (MESS). There was a significant difference between the AUROC of each model (P < 0.0001, DeLong).

Table 7.4: Comparison of the performance of the Bayesian Network prognostic model and the Mangled Extremity Severity Score (MESS) at predicting amputations performed because of a non-viable limb in a cohort of 479 severe lower limb injuries.

Performance Measure	Bayesian Network	MESS
AUROC	0.932 (0.898 – 0.967)	0.723 (0.656 – 0.790)
Sensitivity (%)	90.6 (80.7 – 96.5)	60.3 (46.6 – 72.9)
Specificity (%)	85.5 (81.9 – 88.7)	76.0 (71.6 – 80.0)
DOR	56.8 (43.1 – 74.9)	4.8 (4.0 – 5.8)

Data are presented with 95 percent Confidence Intervals. The operating threshold for the Bayesian Network is a probability > 0.21, and for the MESS, a score ≥ 7. AUROC, Area Under the Receiver Operator Characteristic Curve; DOR, Diagnostic Odds Ratio.

7.4.7 Model presentation and application

A preview version of the complete model is available at http://valinor.agena.co.uk:8080/vbn/vbn.html. Entering predictor values allows the calculation of an individual patients probability of developing a non-viable limb. The tool is specifically designed to provide an individualised risk assessment that allows clinicians, and the patient, to exercise their own informed judgement and choice. The tool is not designed to predict decisions or prescribe treatments at a prespecified threshold.

This version of the model should not be used to inform clinical decisions until its performance in new patients has been validated and the impact of predictions on decision-making and patient outcomes has been assessed.

7.5 Discussion

Key findings

Limb viability is a key outcome following severe lower limb trauma and is central to decisions between attempting salvage and amputation. In a large proportion of cases the risk to limb viability is unclear at the time decisions need to be made, greatly increasing the difficulty of these decisions and potentially jeopardising sound judgement. We have developed a Bayesian Network that can accurately predict limb viability from information that is available at the optimal time for surgical decision-making. This model combines the best available evidence on limb viability prognostic factors with high quality individual patient data from a large cohort study. At the time of initial wound evaluation, this prognostic model can accurately predict the outcome of limb reperfusion and objectively estimate the projected risk to limb viability for an individual injury. Furthermore, the model has significantly superior performance to an existing and well-established decision-support tool, the Mangled Extremity Severity Score (MESS).

Potential applications of findings

The ability to accurately quantify the risk to limb viability for individual injuries has important implications for clinical practice, quality assessment, and future severe lower limb trauma research. Clinically, the Bayesian Network can be used to enhance situational awareness and reduce uncertainty by providing clinicians with a clear estimate of the risk to limb viability at the time treatment decisions need to be made. This information may be weighed-up against other key risks, including the risk to life and estimates of functional outcome, to complement clinical judgement and support rational treatment decisions. Where possible, the model may also be used to provide patients with understandable information regarding the risks associated with their injuries, facilitating shared decision-making and establishing sensible treatment expectations.

Errors or delays in decision-making, and unrealistic treatment expectations, are important causes of poor outcome following severe lower limb trauma (Bondurant et al., 1988, Hansen Jr, 1989). By providing the means to perform an accurate risk assessment, the Bayesian Network can support informed and rational decision-making, which has the potential to improve patient outcomes from these devastating injuries.

For trauma systems, the model may provide a quality assurance tool that supports internal and external benchmarking of performance. By comparing observed and predicted outcomes, an overall assessment of the quality of trauma care can be made. In addition, unexpected outcomes for individual cases can be identified and referred for more detailed interrogation.

The prognostic model may also have a role in trauma research. Risk estimation may help understand differences in case-mix, when comparing different studies. Within studies, cohorts may be catagorised according to risk, to allow more informative analysis. Furthermore, the model could be used to select patients with an appropriate degree of risk to allow more efficient clinical trials.

Model Structure

All non-viable limbs will require amputation. Potential predictors for the Bayesian Network were identified by systematically reviewing the contemporary literature for prognostic factors related to amputation (*Chapter Six*). The identified factors that were mechanistically related to tissue viability were included in the model. A number of identified factors were not included in the model, either because there was insufficient evidence to support a relationship with amputation, or because there was no evidence to support a mechanistic relationship with tissue viability. For example, age was historically believed to be an important prognostic factor for amputation and is included in a number of the lower limb predictive scores and guidelines (ACS, 2005, Gregory et al., 1985,

Johansen et al., 1990, McNamara et al., 1994). However, age was not included in the Bayesian Network. The LEAP study and multiple analyses of the US National Trauma Data Bank have shown that the association between age and primary or secondary amputation is weak (de Mestral et al., 2013, Konstantinidis et al., 2011, MacKenzie et al., 2000, Mullenix et al., 2006). Our meta-analysis is consistent with these findings (*Chapter Six*). Furthermore, there is no direct mechanistic link between age and the risk to tissue viability following injury. Although age may act as a surrogate marker for co-morbidities that influence tissue viability and healing, such as peripheral vascular disease or diabetes, older age and the presence of chronic co-morbidities does not appear to be related to treatment decisions or outcome following severe lower limb trauma (MacKenzie et al., 2000, de Mestral et al., 2013). Similarly, gender and sensory function of the foot where also excluded as model predictors because current evidence shows a weak association with amputation decisions and there is no evidence to suggest a mechanistic relationship with tissue viability (MacKenzie et al., 2000, de Mestral et al., 2013, Bosse et al., 2005, Perkins et al., 2015).

Several factors that were relevant to tissue viability and amputation/salvage decisions were identified, and included in the Bayesian Network. These factors were all related to one of four mechanistic determinants of limb viability, namely: the degree of tissue damage, the degree of ischaemic damage, the adequacy of tissue perfusion, and characteristics of the vascular injury. These four mechanisms formed the core structure of the Bayesian Network.

The network structure was developed in four fragments that relate to the level of the arterial injury (Iliac, Femoral, Popliteal, and Tibial). The Iliac, Femoral, and Popliteal fragments were identical and combined to form a single 'Above-Trifurcation' fragment. Three tibial vessels provide the blood supply to the leg. At this level, limb viability is also related to the number of tibial vessels injured (Burkhardt et al., 2010, Padberg et al., 1992). The network structure at the Tibial level was therefore modified to include an additional variable for the number of tibial arteries injured. This formed the 'Below-

Trifurcation' fragment. The final model consisted of two fragments, 'Above-trifurcation' and 'Below-trifurcation'.

Comparison to existing literature

Several predictive scores have been developed to help surgeons decide which limbs can be salvaged, and which would benefit from early amputation (Gregory et al., 1985, Johansen et al., 1990, Krettek et al., 2001, McNamara et al., 1994, Rajasekaran et al., 2006, Russell et al., 1991, Howe et al., 1987). These scores define successful salvage as a viable limb rather than a functional limb (Dagum et al., 1999, Durham et al., 1996) and apart from the Ganga Hospital Score (Rajasekaran et al., 2006), all are designed for use in patients with lower extremity vascular trauma. None of these scores, however, are accurate enough to reliably support individual treatment decisions (Bonanni et al., 1993, Bosse et al., 2001). In a retrospective validation study, Bonanni et al. (1993) showed low sensitivity of the Mangled Extremity Syndrome Index (six percent), Mangled Extremity Severity Score (22 percent), Predictive Salvage Index (33 percent), and Limb Salvage Index (61 percent) in 58 civilians with severe lower limb injuries. In a prospective and much larger study, the Lower Extremity Assessment Project (LEAP) assessed the clinical utility of the MESS; Predictive Salvage Index (PSI); Limb Salvage Index (LSI); Nerve Injury, Ischemia, Soft-Tissue Injury, Skeletal Injury, Shock, and Age of Patient Score (NISSSA); and Hanover Fracture Scale (HFS) in 556 civilian high-energy lower-extremity injuries. Their analysis demonstrated a relatively high specificity, but again a low sensitivity and only moderate predictive performance for all the scores, confirming the limited clinical usefulness of the current lower-extremity predictive scores in supporting treatment decisions (Bosse et al., 2001).

Despite their moderate performance, the lower limb predictive scores have shown that limb outcome, in terms of amputation or salvage, is predictable and relies on a complex interaction between multiple prognostic factors. A large number of potential prognostic

factors have been described (MacKenzie et al., 2002, Scalea et al., 2012). The strongest seem to be the degree of soft tissue injury and the duration of tissue ischaemia (MacKenzie et al., 2002, Glass et al., 2009, Perkins et al., 2015). These two factors are incorporated in the majority of lower extremity trauma management guidelines and predictive scores (ACS, 2005, Scalea et al., 2012, Nanchahal J, 2009, Gregory et al., 1985, Howe et al., 1987, Johansen et al., 1990, Krettek et al., 2001, McNamara et al., 1994, Russell et al., 1991). The presence of shock has also been shown to be a strong predictor of primary amputation following both military (Brown et al., 2009) and civilian injuries (de Mestral et al., 2013, MacKenzie et al., 2002), and is a key component in many scores (Gregory et al., 1985, Johansen et al., 1990, Krettek et al., 2001, McNamara et al., 1994, Rajasekaran et al., 2006). In addition, a devascularised limb is a fundamental determinant of viability, and is considered in all the lower limb management guidelines and predictive scores (except the Ganga Hospital Score, which is specifically designed for patients without vascular injury) (Nanchahal J, 2009, Scalea et al., 2012, Feliciano et al., 2011).

A number of characteristics of vascular injuries have particular prognostic value. The anatomical level of arterial injury is a well-recognised determinant of the risk to limb viability, with popliteal injuries associated with the highest amputation rates (Kauvar et al., 2011, Mullenix et al., 2006). The number of tibial vessels injured also correlates with the risk to limb viability (Burkhardt et al., 2010, Padberg et al., 1992). Additionally, multiple level arterial injuries have recently been identified as an especially strong predictor of limb viability (Kauvar et al., 2011, Perkins et al., 2015).

An important consideration in the development of the existing lower limb predictive scores was not only the accuracy, but also the simplicity of the tools. Simplicity was required to enhance clinical utility (Johansen et al., 1990). As a result, many of the scores only include factors thought to be the strongest predictors. Simplicity, however, may come at the expense of accuracy, and this may in part explain the moderate performance

of these scores (Bohanec and Bratko, 1994). Due to the widespread availability of computers and improvements in computing power, the simplicity of prognostic scores may be less important in present-day health care than in the 1990's. Indeed, the uptake of computer technology that is now capable of handling powerful mathematical algorithms has the potential to fundamentally change risk assessment and decision-making in health care (Kawamoto et al., 2005, Garg et al., 2005, Bates et al., 2001, Bates et al., 2003).

Mangled Extremity Severity Score

Johansen et al. proposed the MESS in 1990 and it has become the most widely used lower limb predictive score (Johansen et al., 1990). Their aim was to develop a simple scoring system, which could be used following an initial wound examination, to accurately discriminate between salvageable and non-salvageable limbs. MESS consists of four prognostic criteria. However, two of the criteria combine a number of prognostic factors. The skeletal and soft tissue criterion takes into consideration the mechanism of injury, presence of a fracture, degree of soft tissue injury, and degree of wound contamination. Likewise, the limb ischaemia criterion takes into consideration the degree and duration of ischaemia, as well as the perfusion and sensory function of the limb. The remaining criteria consider a single prognostic factor each, namely the degree of shock and the age of the patient. In total, the MESS score considers ten unique prognostic factors grouped into four criteria.

By comparison, our Bayesian Network has many structural similarities to the MESS score. The Bayesian Network also considers ten unique prognostic factors grouped into four broad mechanistic criteria. The strongest predictors in both models are the degree of soft tissue injury, degree of ischaemic damage, and presence of shock. Seven prognostic factors are common to both models. The only MESS predictors not included in the Bayesian Network are patient age, limb sensory function, and the degree of wound contamination. These factors were excluded, as current evidence does not support a prognostic relationship with limb viability.

The models, however, differ in the way in which each tool uses the predictor information to calculate prognosis. The four MESS criteria are categorised, and a point score, increasing with increasing risk, is attached to each category. MESS is a simple summation of these four scores, with a MESS ≥ 7 suggested as predictive of the need for amputation. The Bayesian Network, on the other hand, considers the mechanistic relations between all known prognostic factors to estimate the risk to limb viability.

The predictive performance of the MESS has been extensively evaluated in both civilian (Bonanni et al., 1993, Bosse et al., 2001, Dagum et al., 1999) and military populations (Brown et al., 2009, Sheean et al., 2014). In both of these populations, the MESS had only a moderate ability to predict the need for amputation. This study represents the largest external validation of the MESS score in a Military severe lower limb trauma population, and the findings are consistent with previous validation studies. Overall, the MESS has a sensitivity and positive predictive value of approximately 50 percent and is clearly not accurate enough to be relied upon for treatment decisions (Table 7.5).

Table 7.5: Studies evaluating the performance of the Mangled Extremity Severity Score (MESS) at predicting the need for amputation in civilian and military trauma populations. Pooled predictive performance is calculated for each population. A MESS ≥ 7 is used as the threshold in all studies.

Author	Sample Size	Sensitivity	Specificity	PPV	NPV
Civilian studies					
Bonanni et al. (1993)	58[a]	0.22	0.53	0.17	0.60
Dagum et al. (1999)	40[a]	0.40	0.89	0.33	0.91
Bosse et al. (2001)	556	0.46	0.91	0.65	0.82
Pooled Performance	654	0.43	0.88	0.56	0.81
Military studies					
Brown et al. (2009)	85	0.86	0.84	0.64	0.95
Sheean et al. (2014)	155	0.35	0.88	0.50	0.80
Perkins	479	0.54	0.77	0.35	0.88
Pooled Performance	719	0.53	0.80	0.42	0.87

PPV, Positive Predictive Value; NPV, Negative Predictive Value

[a] Primary amputations excluded

Limitations of the existing scores

Despite the structural similarities, the Bayesian Network has significantly better predictive performance than MESS and the other lower limb predictive scores. Two potentially important reasons for this are worth discussing.

Firstly, the moderate performance of the existing scores in new patients may, in part, be because these scores are over-fitted to their development data. All the scores were developed using relatively small retrospective datasets, and score predictors were selected from these datasets using significance testing or based on expert opinion. These methods have a high risk of selection bias and of producing a score that approximates the characteristics of the development data rather than true relationships (Royston et al., 2009, Steyerberg et al., 2001, Austin and Tu, 2004). This results in a model with

excellent performance in the development data, but is unable to reproduce this performance in new populations. This finding reflects the current evidence-base and strongly suggests that existing scores are over-fitted to their development populations.

Second, simple scores may not be adequate in complex problems. The existing lower limb prediction tools are all simple scoring systems. The ability to weight factors in these scores is limited, and in many cases different factors are given equal weight or the weighting is arbitrary. Furthermore, these scores are unable to account for any interactions between variables. Severe lower limb injuries, however, represent a complex problem. Outcomes and treatment decisions are based on the interactions of multiple risks, each of which is predicted from the interactions of multiple prognostic factors. Some of these factors have a much larger influence than others, and the influence of many factors are correlated. Furthermore, the degree of a factors influence may vary depending on the characteristics of the patient and wound. Simple scores are not able to handle this degree of complexity, and this limitation may manifest in the accuracy of predictions.

Relevance of predicted outcome to Decision-Support

For a prognostic model to be useful in supporting decisions, it should predict an objective and relevant patient outcome that informs the decision-making process. The lower limb scores predict historical amputation decisions, and although amputation is an objective and relevant patient outcome, there are important limitations to predicting a clinicians treatment decisions. First, predicting the decision, rather than presenting the information needed to make a rational decision, does not provide much support to the decision-making process. Second, historical amputation decisions may contain errors that will be learned and propagated by the scores developed from them. It is possible that unnecessary amputations, by today's standards, may have been performed in the populations used to develop the existing lower limb scores (Type 1 errors). For instance, at the time the lower

limb scores were developed an insensate foot was considered one of the most important indications for early amputation, and was strongly associated with amputation decisions (MacKenzie et al., 2002). This was criticised in a seminal study from the Lower Extremity Assessment Project, which demonstrated that initial plantar sensation was not prognostic of long-term sensory status or functional outcome if limb salvage was undertaken (Bosse et al., 2005). It is now accepted that initial plantar sensation is not an indication for lower limb amputation, however, many of the existing scores have been developed to predict these cases (Bosse et al., 2005).

Limbs may also have been classified as successfully salvaged that later required an amputation (Type II errors). The development studies of many predictive scores do not report the duration of follow-up (Gregory et al., 1985, Howe et al., 1987, Russell et al., 1991, McNamara et al., 1994). As demonstrated in *Chapter Three*, a significant proportion of amputations occur months to years after injury. Delayed amputations, if not accounted for, may affect the accuracy of the predictive scores.

Although developing a model to predict historic amputation decisions is convenient, it is quite different from predicting the risks that influence decisions. Limb viability is an objective patient outcome that is central to a large proportion of amputation/salvage decisions. To overcome the limitations of predicting a treatment, and provide more informative decision support, the Bayesian Network was developed to predict a true patient outcome (limb viability) rather than a surrogate marker (the decision to amputate).

7.6 Strengths and Limitations

Strengths

This study has a number of strengths. Most important is that the model is developed to predict an outcome that is central to amputation/salvage decisions, and is often uncertain at the time these decisions need to be made. Second, the structure of the model is derived

from existing knowledge and represents an evidence-based understanding of the factors that affect limb viability following limb-threatening trauma. Knowledge-based methods of developing prognostic models are labour intensive, and therefore rarely used, however, they offer significant benefits over traditional methods including improved face validity, clinical credibility, low risk of over-fitting, and better predictive performance in new patients (generalisability). Third, the models parameters were learned using a method that combines a meta-analysis of contemporary literature and individual patient data from a large cohort study (Yet et al., 2014c). This significantly increases the amount of information available to learn the strength of parameters and the likelihood that parameter estimates will approximate reality. Finally, the prognostic model is developed using Bayesian Networks, a powerful technology that is better suited to handle the multiple interactions and natural variability of complex clinical problems than traditional prognostic modelling methods (Fenton and Neil, 2012b, Van Gerven et al., 2008).

Limitations

This study has a number of limitations that should be acknowledged. Most important, the model's performance has not been validated in new patients. Performance was estimated using the development dataset, and there is a risk this estimate may not be an accurate representation of the models performance in new patients. This risk may be minimal, however, as for the most part the model was developed using existing knowledge. Key steps in model development, which can result in over-fitting (and a biased performance estimate) if based on data, were purposefully performed completely independent of the development dataset. These steps included defining the structure of the model, selecting predictors, and predictor categorisation. The development dataset was only used to estimate parameters where published evidence was lacking. Furthermore, 10-fold cross validation represents the most accurate and least biased method of estimating model performance (Kohavi, 1995). Nonetheless, the model's performance in new patients must be assessed to determine its external validity.

Second, the model's performance was assessed in a US military cohort of severe lower limb injuries, and its performance in civilian or less-resourced settings is unknown. A military cohort may differ in important ways from severe lower limb trauma populations in other settings, and these differences may impact the models accuracy. The model, however, was not designed specifically for military trauma populations, and a wide range of knowledge from diverse populations and settings was used in development. Ultimately, the model's performance will need to be assessed in a variety of settings to determine the generalisability of the tool.

Finally, a degree of measurement error is possible. Classification of limb viability relied on the clinical assessment, and documentation accuracy, of the treating surgeon. A precise and objective measure, such as tissue histology, was not used. Although a single clinical assessment is not perfect, and documentation of findings may be incomplete, the military standard is for all limb amputation decisions to be confirmed by a second surgeon and the indications clearly documented prior to amputation (Clasper, 2007). These steps would enhance measurement accuracy. Indeed, only two cases out of the original cohort of 601 injured limbs (0.003 percent) had unclear documentation of the reason for amputation, and both of these cases were excluded from this study.

CHAPTER EIGHT

Conclusions

8.1 Summary of findings

This thesis presents an improved understanding of decision-making following severe lower limb trauma, and describes the development and validation of novel and accurate prognostic models that can help identify those patients whose limb can be safely and effectively salvaged, and also identify those for whom attempts at limb salvage would be dangerous or potentially fail.

Chapter One describes the relevance of severe lower limb trauma to health and reviews the contemporary management of these injuries. The related management guidelines are summarised, emphasising the treatment goals and key steps in decision-making. It is clear from this review that key decisions are often based on uncertain information, and good judgement relies heavily on clinical experience and intuition. The chapter ends with a description of the tools available to support surgeons with these difficult decisions. A critical appraisal of these tools highlights their methodological weaknesses and their limited ability to support decision-making.

Chapter Two examines fundamental elements of surgical decision-making. Sound judgement in complex problems requires strong situational awareness and an analytical approach to decision-making. Uncertainty is common and can impede situational awareness and make rational decisions difficult. The ability to understand, communicate, and reason with uncertainty is therefore essential, and probability provides a language to accomplish this. Bayes theorem and Bayesian networks provide powerful tools that enable accurate estimates of the probabilities of uncertain states using available information and knowledge. As such, they may provide the ideal tools to improve situational awareness and support rational and evidence-based decisions in complex problems.

Chapter Three establishes the rationale for amputation decisions following severe lower limb trauma. It also demonstrates important characteristics of these decisions including key determinants, and the time frames that decisions are made in. The principal reason for nearly 90 percent of amputations were life-saving haemorrhage control, insufficient tissue for reconstruction, non-viable limb tissue, or functional limitations. Three of these risks (the need for life-saving intervention, predicted limb viability, and predicted limb function) are often uncertain at the optimal time for decision-making, making amputation decisions difficult.

Chapter Four explains the role of Trauma Induced Coagulopathy (TIC) in determining the need for life-saving intervention and validates the clinical relevance of TIC in damage control decision-making and patient outcomes. Evidence supporting the causal mechanisms of TIC was identified and used to develop a Bayesian network prognostic model for the condition. The model is able to provide an early and accurate estimate of an individual patients risk of TIC using routine baseline clinical information.

Chapter Five validates the accuracy and generality of the TIC prognostic model in new patients. The Bayesian network can estimate the risk of a clinically relevant coagulopathy more accurately than any individual clinical predictor, and with comparable accuracy to validated diagnostic tests. The advantage of the model over these diagnostic tests is that it can reliably identify patients at risk of TIC at the right time for decision-making. In addition, the chapter demonstrates the ability of the Bayesian network to handle missing predictor information, a common problem in emergency situations that limits the function of traditional prognostic models.

Chapter Six provides a comprehensive analysis of prognostic factors for amputation following lower limb vascular trauma. In addition, the study determined the absolute and relative amputation risk associated with each prognostic factor.

Chapter Seven uses the evidence established in *Chapter Six* to develop a Bayesian network prognostic model for limb viability. The model is able to accurately predict the outcome of limb reperfusion and objectively estimate the projected risk to limb viability for an individual injury, at the time of initial wound evaluation. Furthermore, the model has significantly better performance than an established and widely used decision-support tool, the Mangled Extremity Severity Score (MESS).

8.2 Strengths and limitations

The main strengths and limitations of each section of this thesis have been acknowledged in the corresponding chapters. There are, however, some important over-arching strengths and limitations that have not been discussed, and are presented here.

Strengths

This thesis demonstrates how Bayesian networks can be used to develop decision-support tools that both support Evidence Based Medicine (EBM) and help overcome some of the difficulties in achieving EBM. The principal aim of EBM is to integrate relevant epidemiological evidence, clinical judgement, and the patients' perspective into clinical decision-making (Sackett et al., 1996). Real EBM makes the care of the individual patients its top priority (Greenhalgh et al., 2014). While EBM has unquestionably advanced health care, it does have some considerable limitations (Tonelli, 1998). Probably the most important criticism of EBM, ironically, is its lack of individualisation. An overemphasis on using one element, the best available evidence, to determine decisions, has shifted the focus of clinical care from what is important to the individual patient towards the average effect in a study population (Tonelli, 1998). As a result, the

contribution from sound clinical judgement and the patients' needs and values has been devalued.

Another notable weakness is that despite the widespread acceptance of EBM principles, the practicalities of how to integrate the different sources of information remain unclear (Engebretsen et al., 2015, Greenhalgh, 1999). No systematic approach to meaningfully draw on, and combine, all elements (epidemiological evidence, clinical expertise and judgement, and patient perspective) have been offered, even though this is fundamental to interpretation and ultimate decision-making. Furthermore, accessing and interpreting the sheer volume of evidence that may be applicable to an individual decision is impractical in daily clinical care (Greenhalgh et al., 2014), and may be impossible in emergency situations.

The Bayesian networks developed in this thesis contribute to EBM in three important ways. Firstly, they allow different types of evidence (including published literature, high-quality data, clinical expertise, and individual patient characteristics) to be integrated and combined in a natural way. Second, they enable individualised, meaningful, and evidence based interpretations of this information. For example, they can be used to quantify the degree of uncertainty and calculate clinically relevant risks for an individual patient. This information supports clinicians, and their patients', in making rational judgements and informed decisions. Third, the network acts as an evidence repository, organising the knowledge related to a particular domain, and allowing efficient access when decision-support is needed.

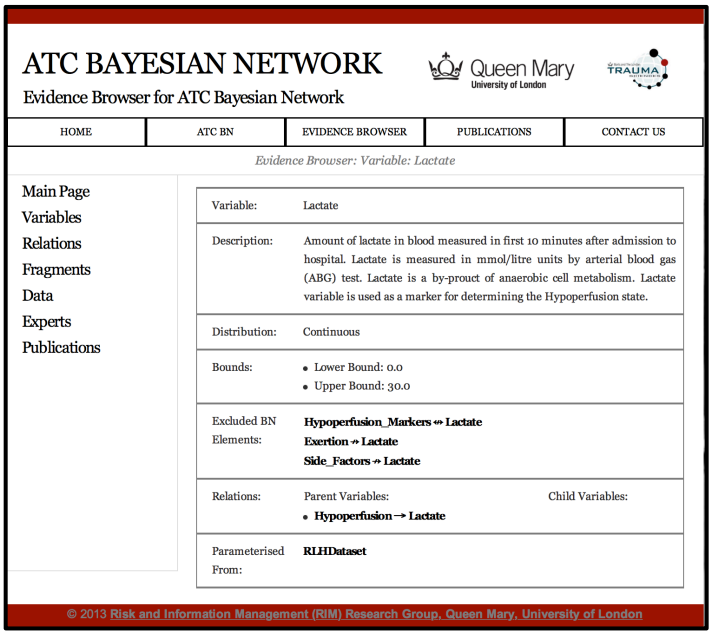
Many prognostic models that are designed to support clinical decision-making are not adopted into routine practice because of a lack of clinical credibility (Wyatt and Altman, 1995). For good reason, doctors are reluctant to use decision-support tools to inform their clinical decisions unless they can believe the model and trust its predictions.

The Bayesian networks developed in this thesis have a number of features that enhance their clinical credibility. First, the models are designed to predict clinically relevant

outcomes using information that is normally available. Second, they are able to generate these predictions at an appropriate time for decision-making. Third, the structure of both models reflects current knowledge and was informed by systematically reviewing the contemporary literature.

In addition, the graphical nature of Bayesian networks is ideally suited to represent this knowledge as well as the models reasoning mechanisms. This allows users to understand and interpret the models structure and logic, something that is not possible with traditional 'black-box' prognostic models. To enhance this capacity, a framework has been developed to organise and present the relevant knowledge and clinical evidence on which the models are based (Yet, 2013, Yet et al., 2014b). This provides users with the ability to browse clear yet detailed information pertaining to the models, including variable definitions, sources of information, and how each piece of evidence relates to the models (Figures 8.1 A and B). Furthermore, the evidence framework will enable upgrading and local modification of the Bayesian networks as new knowledge becomes available and old evidence becomes obsolete.

A) Evidence Browser: Example Variable



B) Evidence Browser: Example Relation

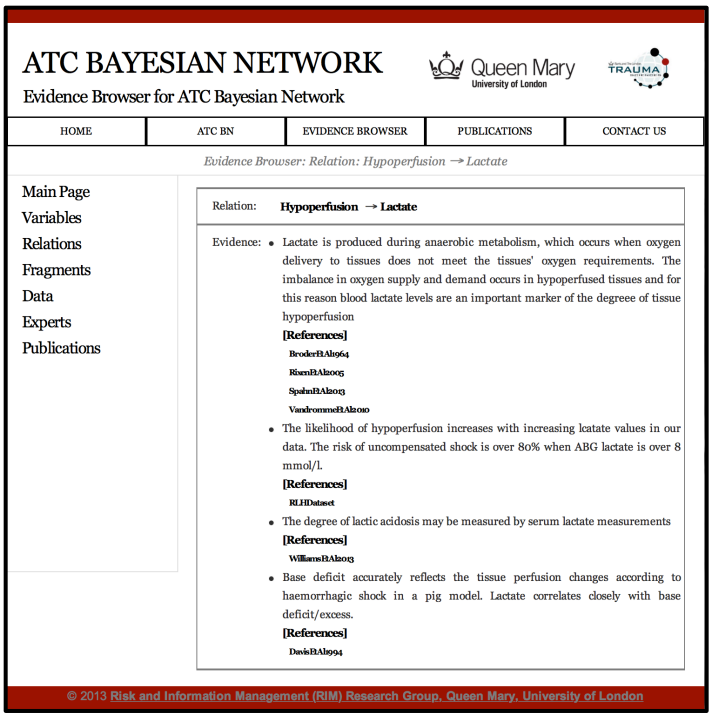


Figure 8.1: Screenshots from the online evidence browser developed by Yet (2013) which is available at http://atcbn.traumamodels.com:8080 showing: A) an example of information on a variable (lactate) in the TIC model, and B) an example of information on a relation (hypoperfusion and lactate) in the TIC model.

Limitations

The aim of this thesis was to develop decision-support tools that are capable of providing the information needed to make informed decisions following severe lower limb trauma. The tools have been specifically designed not to predict decisions or prescribe treatments, but rather to provide relevant individualised risk assessments that allow clinicians, and their patients', to exercise their own judgement and choice. It is assumed that the provision of accurate information will lead to better decisions and improved patient outcomes. However, these assumptions have not been tested in this thesis, and it is not yet known what effect these tools will have on severe lower limb trauma decision-making and outcome.

A number of potential risks and benefits were identified that are key considerations when deliberating the best treatment options. Some are clear at the time of decision-making, while others are uncertain. This thesis has focused on developing models to predict key risks that influence immediate and early decisions, and have a high degree of uncertainty at the time of optimal decision-making. These, however, are not the only risks that are important to consider when making decisions. For example, estimates of the future function of the injured limb, if salvaged or amputated, are important considerations in many situations. Although these models provide accurate information on two important risks (trauma induced coagulopathy and limb viability), decisions should be based on a balance of all the relevant risks in each individual case, and not on the models predictions in isolation.

8.3 Future work

This thesis has developed our overall understanding of surgical decision-making following severe lower limb trauma and why these decisions are often difficult. Rational

treatment decisions depend on an accurate assessment of the risk to life, limb viability, and future limb function; and these risks are frequently uncertain at the time decisions need to be made. This thesis describes the development and validation of two evidence-based prognostic models that enable an accurate and timely assessment of the risk of coagulopathy (the key indication for damage control intervention) and limb viability. Future work should focus on developing a prognostic model for functional outcome. Good quality evidence on functional outcomes following severe lower limb trauma exists (Bosse et al., 2002, MacKenzie et al., 2005, Doukas et al., 2013) and this evidence suggests that functional outcome depends on the combined effect of multiple factors (MacKenzie and Bosse, 2006). It is therefore conceivable that the methods described by Yet et al. (2014a, 2014c) for combining knowledge and data, could be used to develop an accurate Bayesian network prognostic model for functional outcome. Figure 8.1 represents a possible starting point for development of the network structure of such a model.

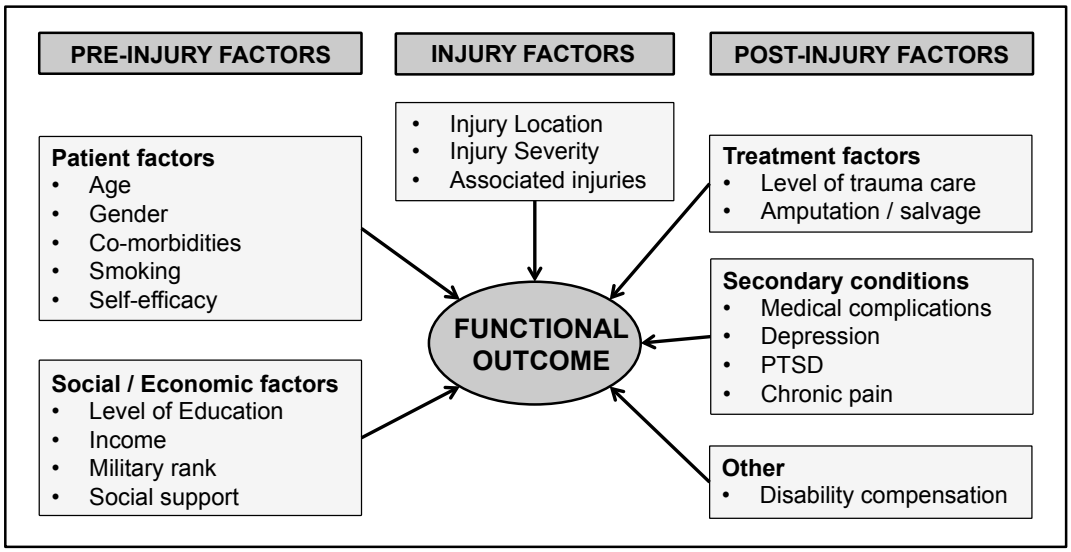


Figure 8.2: Factors influencing the long-term functional outcome of trauma survivors with severe lower limb injuries.

Ideally, a prospective cohort study would be required to collect relevant data for model development; however, it may be possible to identify an existing dataset that includes

high quality information on all relevant factors. Potential datasets include those from the Lower Extremity Assessment Project (LEAP), a multicentre, prospective, observational study (Bosse et al., 2002), and/or the Military Extremity Trauma Amputation/Limb Salvage (METALS) Study, a retrospective cohort study (Doukas et al., 2013).

Future research should also explore methods to optimise the user interface and clinical utility of these tools. An important limitation of many potentially valuable prognostic models is the time it takes to collect and input the required predictor information. Clinicians face increasing time pressures and may be reluctant to use a tool that adds to their workload (Bates et al., 2003). A system that automatically captures predictor information in real-time, from original sources, with automated display of calculations at an appropriate time for decisions, would be ideal. These features are strongly associated with improved clinical practice (Kawamoto et al., 2005). However, this requires clinical information to be routinely recorded in an electronic format. While some predictors, such as vital signs and blood analyses, are already captured electronically, others, such as history and examination findings, are still frequently recorded in hand-written notes. There is, however, a worldwide shift from paper-based to electronic patient records, with the National Health Service in England aiming to be paperless by 2018 (DOH, 2013). The development of suitable electronic patient records that can integrate computerised decision-support tools, such as the Bayesian networks developed in this thesis, have the potential to significantly improve health care (Bates et al., 2003, Bates and Gawande, 2003, Kawamoto et al., 2005).

Clinically useful methods of presenting the models probability estimates also requires further exploration. Although both models provide accurate predictions of clinically relevant patient risks, the significance of an absolute value may not be immediately apparent to the user.

Future research should define clinically relevant risk categories that support clinicians, and their patients', in making informed decisions. In addition, relevant thresholds to guide critical interventions, such as activation of a Major Haemorrhage protocol or initiation of a damage control approach to surgery, should be investigated from a patient outcome, resource use, and cost perspective.

Finally, the ultimate aim of the decision-support tools developed in this thesis is to improve the quality of trauma care and patient outcomes. A well-conducted clinical trial, designed to measure the impact that providing predictions has on decision-making, quality of care, and patient outcomes, compared to usual care, is warranted. The ideal methodology would be a randomised control trial and, as severe lower limb injuries are relatively rare, a multicentre trial would be necessary to recruit sufficient participants in an efficient timeframe. Such a trial would also help determine the role of knowledge-based Bayesian networks as tools to support individualised and evidence based decisions in complex clinical problems.

8.4 Conclusions

This thesis has advanced the understanding of surgical decision-making following severe lower limb trauma, and presents two novel prognostic models to support these difficult decisions. These tools allow an accurate assessment of critical risks in individual cases. This information may help clinicians and patients understand their situation, and supports rational judgement on the most beneficial therapy. Prospective evaluation of the impact of these tools on decision-making and patient outcomes is needed. In the future, prognostic models like these Bayesian networks may be key to enabling clinicians to make individualised and evidence-based treatment decisions.

REFERENCES

ACS. (2005). Management of Complex Extremity Trauma. American College of Surgeons Committee on Trauma.

ACS. (2012). *ATLS, Advanced Trauma Life Support for doctors,* Chicago, American College of Surgeons.

Adrie, C., Monchi, M., Laurent, I., Um, S., Yan, S. B., Thuong, M., Cariou, A., Charpentier, J. & Dhainaut, J. F. (2005). Coagulopathy after successful cardiopulmonary resuscitation following cardiac arrest: implication of the protein C anticoagulant pathway. *Journal of the American College of Cardiology,* 46**,** 21-28.

Affonseca, C. A., Carvalho, L. F., Guerra, S. D., Ferreira, A. R. & Goulart, E. M. (2007). Coagulation disorder in children and adolescents with moderate to severe traumatic brain injury. *Jornal de Pediatria,* 83**,** 274-282.

Aitkin, M., Francis, B., Hinde, J. & Darnell, R. (2009). Statistical modelling and inference. *Statistical modelling in R.* Oxford University Press.

Altman, D. (2009). Prognostic models: a methodological framework and review of models for breast cancer. *Cancer Investigation,* 27**,** 235.

Altman, D. G. (2001). Systematic reviews of evaluations of prognostic variables. *British Medical Journal,* 323**,** 224-228.

Altman, D. G. & Royston, P. (2006). The cost of dichotomising continuous variables. *British Medical Journal,* 332**,** 1080.

Altman, D. G., Vergouwe, Y., Royston, P. & Moons, K. G. M. (2009). Prognosis and prognostic research: validating a prognostic model. *British Medical Journal,* 338**,** b605.

Anderson, W. D., Stewart, K. J., Wilson, Y. & Quaba, A. A. (2002). Skin grafts for the salvage of degloved below-knee amputation stumps. *British Journal of Plastic Surgery,* 55**,** 320-323.

Anglen, J. O. (2005). Comparison of soap and antibiotic solutions for irrigation of lower-limb open fracture wounds. A prospective, randomized study. *Journal of Bone & Joint Surgery, American volume,* 87**,** 1415-1422.

Asensio, J. A., Kuncir, E. J., Garcia-Nunez, L. M. & Petrone, P. (2006). Femoral vessel injuries: analysis of factors predictive of outcomes. *Journal of the American College of Surgeons,* 203**,** 512-520.

Aucar, J. A. & Hirshberg, A. (1997). Damage control for vascular injuries. *Surgical Clinics of North America,* 77**,** 853-862.

Aucar, J. A., Norman, P., Whitten, E., Granchi, T. S., Liscum, K. R., Wall, M. J. & Mattox, K. L. (2003). Intraoperative detection of traumatic coagulopathy using the activated coagulation time. *Shock,* 19**,** 404-407.

Austin, P. C. & Tu, J. V. (2004). Automated variable selection methods for logistic regression produced unstable models for predicting acute myocardial infarction mortality. *Journal of Clinical Epidemiology,* 57**,** 1138-1146.

Bach, S., Noreng, M. F. & Tjellden, N. U. (1988). Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. *Pain,* 33**,** 297-301.

Baker, S. P., o'Neill, B., Haddon Jr, W. & Long, W. B. (1974). The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *Journal of Trauma - Injury, Infection and Critical Care,* 14**,** 187-196.

Balogh, Z. J., Reumann, M. K., Gruen, R. L., Mayer-Kuckuk, P., Schuetz, M. A., Harris, I. A., Gabbe, B. J. & Bhandari, M. (2012). Advances and future directions for management of trauma patients with musculoskeletal injuries. *Lancet,* 380**,** 1109-1119.

Banner, D. W., D'Arcy, A., Chene, C., Winkler, F. K., Guha, A., Konigsberg, W. H., Nemerson, Y. & Kirchhofer, D. (1996). The crystal structure of the complex of blood coagulation factor VIIa with soluble tissue factor. *Nature,* 380**,** 41-46.

Barr, J., Cherry, K. J. & Rich, N. M. (2015). Vascular Surgery in World War II: The Shift to Repairing Arteries. *Annals of Surgery,* Publish Ahead of Print.

Barros D'Sa, A. A., Harkin, D. W., Blair, P. H., Hood, J. M. & McIlrath, E. (2006). The Belfast approach to managing complex lower limb vascular injuries. *European Journal of Vascular and Endovascular Surgery,* 32**,** 246-256.

Bates, D. W., Cohen, M., Leape, L. L., Overhage, J. M., Shabot, M. M. & Sheridan, T. (2001). Reducing the frequency of errors in medicine using information technology. *Journal of the American Medical Informatics Association,* 8**,** 299-308.

Bates, D. W. & Gawande, A. A. (2003). Improving safety with information technology. *New England Journal of Medicine,* 348**,** 2526-2534.

Bates, D. W., Kuperman, G. J., Wang, S., Gandhi, T., Kittler, A., Volk, L., Spurr, C., Khorasani, R., Tanasijevic, M. & Middleton, B. (2003). Ten commandments for effective clinical decision support: making the practice of evidence-based medicine a reality. *Journal of the American Medical Informatics Association,* 10**,** 523-530.

Bayes, T. & Price, R. (1763). An essay towards solving a problem in the doctrine of chances. *Philosophical Transactions***,** 370-418.

Beekley, A. C., Sebesta, J. A., Blackbourne, L. H., Herbert, G. S., Kauvar, D. S., Baer, D. G., Walters, T. J., Mullenix, P. S., Holcomb, J. B. & Group, s. C. S. H. R. (2008). Prehospital tourniquet use in Operation Iraqi Freedom: effect on hemorrhage control and outcomes. *Journal of Trauma - Injury, Infection and Critical Care,* 64**,** S28-S37.

Bergner, M., Bobbitt, R. A., Carter, W. B. & Gilson, B. S. (1981). The Sickness Impact Profile: development and final revision of a health status measure. *Medical Care***,** 787-805.

Bhandari, M., Guyatt, G. H., Swiontkowski, M. F. & Schemitsch, E. H. (2001). Treatment of open fractures of the shaft of the tibia A SYSTEMATIC OVERVIEW AND META-ANALYSIS. *Journal of Bone & Joint Surgery, British Volume,* 83**,** 62-68.

Blaisdell, F. W. (2002). The pathophysiology of skeletal muscle ischemia and the reperfusion syndrome: a review. *Cardiovascular Surgery,* 10**,** 620-630.

Bohanec, M. & Bratko, I. (1994). Trading accuracy for simplicity in decision trees. *Machine Learning,* 15**,** 223-250.

Bolliger, D., Szlam, F., Levy, J. H., Molinaro, R. J. & Tanaka, K. A. (2010). Haemodilution-induced profibrinolytic state is mitigated by fresh-frozen plasma: Implications for early haemostatic intervention in massive haemorrhage. *British Journal of Anaesthesia,* 104**,** 318-325.

Bonanni, F., Rhodes, M. & Lucke, J. F. (1993). The futility of predictive scoring of mangled lower extremities. *Journal of Trauma - Injury, Infection and Critical Care,* 34**,** 99-104.

Bondurant, F. J., Cotler, H. B., Buckle, R., Miller-Crotchett, P. & Browner, B. D. (1988). The medical and economic impact of severely injured lower extremities. *Journal of Trauma - Injury, Infection and Critical Care,* 28**,** 1270-1273.

Bosse, M. J., MacKenzie, E. J., Kellam, J. F., Burgess, A. R., Webb, L. X., Swiontkowski, M. F., Sanders, R. W., Jones, A. L., McAndrew, M. P., Patterson, B. M., et al. (2001). A prospective evaluation of the clinical utility of the lower-extremity injury-severity scores. *Journal of Bone & Joint Surgery, American volume,* 83-A**,** 3-14.

Bosse, M. J., MacKenzie, E. J., Kellam, J. F., Burgess, A. R., Webb, L. X., Swiontkowski, M. F., Sanders, R. W., Jones, A. L., McAndrew, M. P., Patterson, B. M., et al. (2002). An analysis of outcomes of reconstruction or amputation after leg-threatening injuries. *New England Journal of Medicine,* 347**,** 1924-1931.

Bosse, M. J., McCarthy, M. L., Jones, A. L., Webb, L. X., Sims, S. H., Sanders, R. W., MacKenzie, E. J. & Lower Extremity Assessment Project Study, G. (2005). The

insensate foot following severe lower extremity trauma: an indication for amputation? *Journal of Bone & Joint Surgery, American volume,* 87**,** 2601-2608.

Bourke, H. E., Yelden, K. C., Robinson, K. P., Sooriakumaran, S. & Ward, D. A. (2010). Is revision surgery following lower-limb amputation a worthwhile procedure? A retrospective review of 71 cases. *Injury,* 42**,** 660-666.

Brazil, E. V. & Coats, T. J. (2000). Sonoclot coagulation analysis of in-vitro haemodilution with resuscitation solutions. *Journal of the Royal Society of Medicine,* 93**,** 507-510.

Brier, G. W. (1950). Verification of forecasts expressed in terms of probability. *Monthly Weather Review,* 78**,** 1-3.

Brohi, K. (2011). Prediction of acute traumatic coagulopathy and massive transfusion - Is this the best we can do? *Resuscitation,* 82**,** 1128-1129.

Brohi, K., Cohen, M. J. & Davenport, R. A. (2007a). Acute coagulopathy of trauma: mechanism, identification and effect. *Current Opinion in Critical Care,* 13**,** 680-685.

Brohi, K., Cohen, M. J., Ganter, M. T., Matthay, M. A., Mackersie, R. C. & Pittet, J. F. (2007b). Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? *Annals of Surgery,* 245**,** 812-818.

Brohi, K., Cohen, M. J., Ganter, M. T., Schultz, M. J., Levi, M., Mackersie, R. C. & Pittet, J. F. (2008). Acute coagulopathy of trauma: Hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *Journal of Trauma - Injury, Infection and Critical Care,* 64**,** 1211-1217.

Brohi, K., Cole, E. & Hoffman, K. (2011). Improving outcomes in the early phases after major trauma. *Current Opinion in Critical Care,* 17**,** 515-519.

Brohi, K., Singh, J., Heron, M. & Coats, T. (2003). Acute traumatic coagulopathy. *Journal of Trauma - Injury, Infection and Critical Care,* 54**,** 1127-1130.

Brophy, D. F., Contaifer, D., Mohammed, B. M., Newton, J. C., Martin, E. J., Brophy, G., White, N. J., Reynolds, P. S., Song, J. & Ward, K. R. (2013). Defining platelet function in polytrauma patients upon admission to the emergency department. *Journal of Thrombosis and Haemostasis,* 11**,** 743.

Brown, E. S., Fulton, M. K., Wilkeson, A. & Petty, F. (2000). The psychiatric sequelae of civilian trauma. *Comprehensive Psychiatry,* 41**,** 19-23.

Brown, K. V., Murray, C. K. & Clasper, J. C. (2010). Infectious complications of combat-related mangled extremity injuries in the British military. *Journal of Trauma - Injury, Infection and Critical Care,* 69**,** S109-S115.

Brown, K. V., Ramasamy, A., McLeod, J., Stapley, S. & Clasper, J. C. (2009). Predicting the need for early amputation in ballistic mangled extremity injuries. *Journal of Trauma - Injury, Infection and Critical Care,* 66**,** S93-97.

Brummel-Ziedins, K., Whelihan, M. F., Ziedins, E. G. & Mann, K. G. (2006). The resuscitative fluid you choose may potentiate bleeding. *Journal of Trauma - Injury, Infection and Critical Care,* 61**,** 1350-1358.

Bryant, G. D. & Norman, G. R. (1980). Expressions of probability: words and numbers. *New England Journal of Medicine,* 302**,** 411.

Burg, A., Nachum, G., Salai, M., Haviv, B., Heller, S., Velkes, S. & Dudkiewicz, I. (2009). Treating civilian gunshot wounds to the extremities in a level 1 trauma center: Our experience and recommendations. *Israel Medical Association Journal,* 11**,** 546-551.

Burkhardt, G. E., Cox, M., Clouse, W. D., Porras, C., Gifford, S. M., Williams, K., Propper, B. W. & Rasmussen, T. E. (2010). Outcomes of selective tibial artery repair following combat-related extremity injury. *Journal of Vascular Surgery,* 52**,** 91-96.

Burruss, S., Andakyan, A., Romanov, S., Semiletova, N. & Cryer, H. (2012). Effect of protein C gene mutation on coagulation and inflammation in hemorrhagic shock. *Journal of Surgical Research,* 175**,** 18-23.

Burton, P. R., Gurrin, L. C. & Campbell, M. J. (1998). Clinical significance not statistical significance: a simple Bayesian alternative to p values. *Journal of Epidemiology and Community Health,* 52**,** 318-323.

Busse, J. W., Jacobs, C. L., Swiontkowski, M. F., Bosse, M. J., Bhandari, M. & Evidence-Based Orthopaedic Trauma Working, G. (2007). Complex limb salvage or early amputation for severe lower-limb injury: a meta-analysis of observational studies. *Journal of Orthopaedic Trauma,* 21**,** 70-76.

Callcut, R. A., Acher, C. W., Hoch, J., Tefera, G., Turnipseed, W. & Mell, M. W. (2009). Impact of intraoperative arteriography on limb salvage for traumatic popliteal artery injury. *Journal of Trauma - Injury, Infection and Critical Care,* 67**,** 252-259.

Cap, A. P. & Spinella, P. C. (2011). Severity of head injury is associated with increased risk of coagulopathy in combat casualties. *Journal of Trauma - Injury, Infection and Critical Care,* 71**,** S78-S81.

Carrick, M. M., Tyroch, A. H., Youens, C. A., Handley, T., Wiles, I. I. I. C. E., Davis, K. A. & Tarui, T. (2005). Subsequent development of thrombocytopenia and coagulopathy in moderate and severe head injury: Support for serial laboratory examination. *Journal of Trauma - Injury, Infection and Critical Care,* 58**,** 725-730.

Casscells, W., Schoenberger, A. & Graboys, T. B. (1978). Interpretation by physicians of clinical laboratory results. *New England Journal of Medicine,* 299**,** 999-1001.

Casstevens, E. C., MacLeod, J. B. & Shaz, B. (2010). Early trauma induced coagulopathy (ETIC) is associated with an increase in complications post-injury. *Transfusion,* 50**,** 36A-37A.

Castillo, R. C., Mackenzie, E. J., Bosse, M. J. & Group, L. S. (2011). Orthopaedic trauma clinical research: is 2-year follow-up necessary? Results from a longitudinal study of severe lower extremity trauma. *Journal of Trauma - Injury, Infection and Critical Care,* 71**,** 1726-1731.

Castillo, R. C., MacKenzie, E. J., Wegener, S. T., Bosse, M. J. & Group, L. S. (2006). Prevalence of chronic pain seven years following limb threatening lower extremity trauma. *Pain,* 124**,** 321-329.

CDC. (2010). Injury prevention and control: data and statistics. The ten leading causes of death and injury.: Centres for disease control and prevention.

Chandran, A., Hyder, A. A. & Peek-Asa, C. (2010). The global burden of unintentional injuries and an agenda for progress. *Epidemiologic Reviews,* 32**,** 110-120.

Chang, R. (2002). The Possibility of Parity*. *Ethics,* 112**,** 659-688.

Chang, R. (2014). *Making comparisons count*, Routledge.

Cheddie, S., Muckart, D. J. & Hardcastle, T. C. (2013). Base deficit as an early marker of coagulopathy in trauma. *South African Journal of Surgery,* 51**,** 88-90.

Chesebro, B. B., Rahn, P., Carles, M., Esmon, C. T., Xu, J., Brohi, K., Frith, D., Pittet, J. F. & Cohen, M. J. (2009). Increase in activated protein C mediates acute traumatic coagulopathy in mice. *Shock,* 32**,** 659-665.

Chhabra, G., Sharma, S., Subramanian, A., Agrawal, D., Sinha, S. & Mukhopadhyay, A. K. (2013). Coagulopathy as prognostic marker in acute traumatic brain injury. *Journal of Emergencies, Trauma and Shock,* 6**,** 180-185.

Clasper, J. (2007). Amputations of the lower limb: a multidisciplinary consensus. *Journal of the Royal Army Medical Corps,* 153**,** 172-174.

Coats, T. J., Brazil, E., Heron, M. & MacCallum, P. K. (2006). Impairment of coagulation by commonly used resuscitation fluids in human volunteers. *Emergency Medicine Journal,* 23**,** 846-849.

Cohen, M. J., Brohi, K., Ganter, M. T., Manley, G. T., Mackersie, R. C. & Pittet, J. F. (2007). Early coagulopathy after traumatic brain injury: the role of hypoperfusion and

the protein C pathway. *Journal of Trauma - Injury, Infection and Critical Care,* 63**,** 1254-1262.

Cohen, M. J., Call, M., Nelson, M., Calfee, C. S., Esmon, C. T., Brohi, K. & Pittet, J. F. (2012). Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. *Annals of Surgery,* 255**,** 379-385.

Cohen, M. J., Kutcher, M., Redick, B., Nelson, M., Call, M., Knudson, M., Schreiber, M. A., Bulger, E. M., Muskat, P., Alarcon, L. H., et al. (2013). Clinical and mechanistic drivers of acute traumatic coagulopathy. *Journal of Trauma and Acute Care Surgery,* 75**,** S40-S47.

Cordts, M. R., Parreira, J. G., Perlingeiro, J. A., Solda, S. C., Campos, T. & Assef, J. C. (2011). Pelvic fractures as a marker of injury severity in trauma patients. *Revista do Colegio Brasileiro de Cirurgioes,* 38**,** 310-316.

Cosgriff, N., Moore, E. E., Sauaia, A., Kenny-Moynihan, M., Burch, J. M. & Galloway, B. (1997). Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. *Journal of Trauma - Injury, Infection and Critical Care,* 42**,** 857-861.

Cotton, B. A., Gunter, O. L., Isbell, J., Au, B. K., Robertson, A. M., Morris Jr, J. A., Jacques, P. S. & Young, P. P. (2008). Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. *Journal of Trauma - Injury, Infection and Critical Care,* 64**,** 1177-1183.

Cotton, B. A., Sixta, S. L., Wade, C. E., Holcomb, J. B. & Matijevic-Aleksic, N. (2011). Mechanistic determinants of the acute coagulopathy of trauma (ACoT) in patients undergoing emergency surgery. *Blood,* 118.

Couch, K. S. & Stojadinovic, A. (2011). Negative-pressure wound therapy in the military: lessons learned. *Plastic and Reconstructive Surgery,* 127 Suppl 1**,** 117S-130S.

Coulter, A. & Collins, A. (2011). Making shared decision-making a reality. *No decision about me, without me. The King's Fund*.

Coupland, R. M. (1989). Technical aspects of war wound excision. *British Journal of Surgery,* 76**,** 663-667.

Croskerry, P. (2013). From mindless to mindful practice—cognitive bias and clinical decision making. *New England Journal of Medicine,* 368**,** 2445-2448.

Crowley, D. J., Kanakaris, N. K. & Giannoudis, P. V. (2007a). Debridement and wound closure of open fractures: the impact of the time factor on infection rates. *Injury,* 38**,** 879-889.

Crowley, D. J., Kanakaris, N. K. & Giannoudis, P. V. (2007b). Irrigation of the wounds in open fractures. *Journal of Bone & Joint Surgery, British Volume,* 89**,** 580-585.

Dagum, A. B., Best, A. K., Schemitsch, E. H., Mahoney, J. L., Mahomed, M. N. & Blight, K. R. (1999). Salvage after severe lower-extremity trauma: are the outcomes worth the means? *Plastic and Reconstructive Surgery,* 103**,** 1212-1220.

Dar, A. M., Ahanger, A. G., Wani, R. A., Bhat, M. A., Lone, G. N. & Shah, S. H. (2003). Popliteal artery injuries: the Kashmir experience. *Journal of Trauma - Injury, Infection and Critical Care,* 55**,** 362-365.

Darlington, D., Fedyk, C., Scherer, M., Kheirabadi, B., Pusateri, A., Wade, C., Cap, A. & Dubick, M. (2010). Hemodilution effects coagulation of human blood ex vivo. *Critical Care Medicine,* 38.

Darlington, D. N., Craig, T., Gonzales, M. D., Schwacha, M. G., Cap, A. P. & Dubick, M. A. (2012a). Development of a rat model of acute coagulopathy of trauma. *Shock,* 37.

Darlington, D. N., Craig, T., Gonzales, M. D., Schwacha, M. G., Cap, A. P. & Dubick, M. A. (2013). Acute coagulopathy of trauma in the rat. *Shock,* 39**,** 440-446.

Darlington, D. N., Kheirabadi, B. S., Delgado, A. V., Scherer, M. R., Martini, W. Z. & Dubick, M. A. (2011). Coagulation changes to systemic acidosis and bicarbonate

correction in swine. *Journal of Trauma - Injury, Infection and Critical Care,* 71**,** 1271-1277.

Darlington, D. N., Kremenevskiy, I., Pusateri, A. E., Scherer, M. R., Fedyk, C. G., Kheirabaldi, B. S., Delgado, A. V. & Dubick, M. A. (2012b). Effects of In vitro hemodilution, hypothermia and rFVIIa addition on coagulation in human blood. *International Journal of Burns & Trauma,* 2**,** 42-50.

Davenport, R., Manson, J., De'Ath, H., Platton, S., Coates, A., Allard, S., Hart, D., Pearse, R., Pasi, K. J., MacCallum, P., et al. (2011). Functional definition and characterization of acute traumatic coagulopathy. *Critical Care Medicine,* 39**,** 2652-2658.

Davidovic, L. B., Cinara, I. S., Ille, T., Kostic, D. M., Dragas, M. V. & Markovic, D. M. (2005). Civil and war peripheral arterial trauma: review of risk factors associated with limb loss. *Vascular,* 13**,** 141-147.

Davis, J. W., Parks, S. N., Kaups, K. L., Gladen, H. E. & O'Donnell-Nicol, S. (1996). Admission base deficit predicts transfusion requirements and risk of complications. *Journal of Trauma - Injury, Infection and Critical Care,* 41**,** 769-774.

de Mestral, C., Sharma, S., Haas, B., Gomez, D. & Nathens, A. B. (2013). A contemporary analysis of the management of the mangled lower extremity. *Journal of Trauma and Acute Care Surgery,* 74**,** 597-603.

DeBakey, M. E. & Simeone, F. A. (1946). Battle injuries of the arteries in World War II: an analysis of 2,471 cases. *Annals of Surgery,* 123**,** 534.

Deeks, J. J. (2001). Systematic reviews of evaluations of diagnostic and screening tests. *Systematic Reviews in Health Care: Meta-Analysis in Context, Second Edition.*

Degiannis, E., Bowley, D. M., Bode, F., Lynn, W. R., Glapa, M., Baxter, S., Shapey, J., Smith, M. D. & Doll, D. (2007). Ballistic arterial trauma to the lower extremity: recent South African experience. *American Surgeon,* 73**,** 1136-1139.

DeLong, E. R., DeLong, D. M. & Clarke-Pearson, D. L. (1988). Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics,* 44**,** 837-845.

Dempster, A. P., Laird, N. M. & Rubin, D. B. (1977). Maximum likelihood from incomplete data via the EM algorithm. *Journal of the Royal Statistical Society. Series B (Methodological)***,** 1-38.

Dickneite, G., Dorr, B., Kaspereit, F. & Tanaka, K. A. (2010). Prothrombin complex concentrate versus recombinant factor vIIa for reversal of hemodilutional coagulopathy in a porcine trauma model. *Journal of Trauma - Injury, Infection and Critical Care,* 68**,** 1151-1157.

Dickneite, G. & Pragst, I. (2009). Prothrombin complex concentrate vs fresh frozen plasma for reversal of dilutional coagulopathy in a porcine trauma model. *British Journal of Anaesthesia,* 102**,** 345-354.

Dickson, E. J. & Chong, P. S. (2009). Patient assessment and surgical risk. *In:* Paterson-Brown, S. (ed.) *Core Topics in General & Emergency Surgery: Companion to Specialist Surgical Practice.* Fourth ed.: Elsevier Health Sciences.

DOH. (2013). The Digital Challenge: How a paperless NHS will improve services. Available: https://digitalchallenge.dh.gov.uk/2013/01/16/paperless/ [Accessed 08/09/2015].

Dorlac, W. C., DeBakey, M. E., Holcomb, J. B., Fagan, S. P., Kwong, K. L., Dorlac, G. R., Schreiber, M. A., Persse, D. E., Moore, F. A. & Mattox, K. L. (2005). Mortality from isolated civilian penetrating extremity injury. *Journal of Trauma - Injury, Infection and Critical Care,* 59**,** 217-222.

Doukas, W. C., Hayda, R. A., Frisch, H. M., Andersen, R. C., Mazurek, M. T., Ficke, J. R., Keeling, J. J., Pasquina, P. F., Wain, H. J., Carlini, A. R., et al. (2013). The Military Extremity Trauma Amputation/Limb Salvage (METALS) study: outcomes of amputation versus limb salvage following major lower-extremity trauma. *Journal of Bone & Joint Surgery, American volume,* 95**,** 138-145.

Dubick, M., Scherer, M., Darlington, D. & Kheriabadi, B. (2009). Effects of acidosis and pH correction on thrombin generation in a swine hemorrhage model. *Critical Care Medicine,* 37.

Duchesne, J. C., Islam, T. M., Stuke, L., Timmer, J. R., Barbeau, J. M., Marr, A. B., Hunt, J. P., Dellavolpe, J. D., Wahl, G., Greiffenstein, P., et al. (2009). Hemostatic resuscitation during surgery improves survival in patients with traumatic-induced coagulopathy. *Journal of Trauma - Injury, Infection and Critical Care,* 67**,** 33-37; discussion 37-39.

Duchesne, J. C., McSwain Jr, N. E., Cotton, B. A., Hunt, J. P., Dellavolpe, J., Lafaro, K., Marr, A. B., Gonzalez, E. A., Phelan, H. A. & Bilski, T. (2010a). Damage control resuscitation: the new face of damage control. *Journal of Trauma and Acute Care Surgery,* 69**,** 976-990.

Duchesne, J. C., McSwain, N. E., Jr., Cotton, B. A., Hunt, J. P., Dellavolpe, J., Lafaro, K., Marr, A. B., Gonzalez, E. A., Phelan, H. A., Bilski, T., et al. (2010b). Damage control resuscitation: the new face of damage control. *Journal of Trauma - Injury, Infection and Critical Care,* 69**,** 976-990.

Dufour D, J. S. K., Owen-Smith M, Salmela J, Stening F, Zetterstrom B. (1998). *Surgery for victims of war,* Geneva, International Committee of the Red Cross.

Durham, R. M., Mistry, B. M., Mazuski, J. E., Shapiro, M. & Jacobs, D. (1996). Outcome and utility of scoring systems in the management of the mangled extremity. *The American Journal of Surgery,* 172**,** 569-574.

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., Mallett, O., Zubko, T., Oetjen-Gerdes, L. & Rasmussen, T. E. (2012). Death on the battlefield (2001–2011): implications for the future of combat casualty care. *Journal of Trauma and Acute Care Surgery,* 73**,** S431-S437.

Egger, M., Davey Smith, G., Schneider, M. & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal,* 315**,** 629-634.

Ekim, H., Kutay, V., Demirbag, R., Hazar, A. & Karadag, M. (2004). Management of the lower extremity arterial injuries. *Eastern Journal of Medicine,* 9**,** 39-44.

Ekim, H. & Odabasi, D. (2010). Management of combined femoral artery and vein injuries. *Pakistan Journal of Medical Sciences,* 26**,** 96-101.

Engebretsen, E., Vøllestad, N. K., Wahl, A. K., Robinson, H. S. & Heggen, K. (2015). Unpacking the process of interpretation in evidence‐based decision making. *Journal of Evaluation in Clinical Practice,* 21**,** 529-531.

Engels, P. T., Rezende-Neto, J. B., Al, M., Scarpelini, S., Rizoli, S. B. & Tien, H. C. (2011). The natural history of trauma-related coagulopathy: Implications for treatment. *Journal of Trauma - Injury, Infection and Critical Care,* 71**,** S448-S455.

Engstrom, M., Schott, U., Romner, B. & Reinstrup, P. (2006). Acidosis impairs the coagulation: A thromboelastographic study. *Journal of Trauma - Injury, Infection and Critical Care,* 61**,** 624-628.

Erdmann, D., Sundin, B. M., Yasui, K., Wong, M. S. & Levin, L. S. (2002). Microsurgical free flap transfer to amputation sites: indications and results. *Annals of Plastic Surgery,* 48**,** 167-172.

Evans, J. S. B. T. (2003). In two minds: dual-process accounts of reasoning. *Trends in Cognitive Sciences,* 7**,** 454-459.

Evans, S. A., Airey, M. C., Chell, S. M., Connelly, J. B., Rigby, A. S. & Tennant, A. (2003). Disability in young adults following major trauma: 5 year follow up of survivors. *BMC Public Health,* 3**,** 8.

Feliciano, D. (2002). Management of the Mangled Extremity. American College of Surgeons.

Feliciano, D. V. (2010). Management of peripheral arterial injury. *Current Opinion in Critical Care,* 16**,** 602-608.

Feliciano, D. V., Mattox, K. L., Graham, J. M. & Bitondo, C. G. (1985). Five-year experience with PTFE grafts in vascular wounds. *Journal of Trauma - Injury, Infection and Critical Care,* 25**,** 71-82.

Feliciano, D. V., Moore, E. E., West, M. A., Moore, F. A., Davis, J. W., Cocanour, C. S., Scalea, T. M. & McIntyre, R. C., Jr. (2013). Western Trauma Association Critical Decisions in Trauma: Evaluation and management of peripheral vascular injury, Part II. *Journal of Trauma and Acute Care Surgery,* 75**,** 391-397.

Feliciano, D. V., Moore, F. A., Moore, E. E., West, M. A., Davis, J. W., Cocanour, C. S., Kozar, R. A. & McIntyre, R. C., Jr. (2011). Evaluation and management of peripheral vascular injury. Part 1. Western Trauma Association/critical decisions in trauma. *Journal of Trauma - Injury, Infection and Critical Care,* 70**,** 1551-1556.

Fenton, N. & Neil, M. (2012a). The need for causal, explanatory models in risk assessment. *Risk Assessment and Decision Analysis with Bayesian Networks.* CRC Press.

Fenton, N. & Neil, M. (2012b). *Risk assessment and decision analysis with Bayesian networks*, CRC Press.

Fergason, J., Keeling, J. J. & Bluman, E. M. (2010). Recent advances in lower extremity amputations and prosthetics for the combat injured patient. *Foot And Ankle Clinics,* 15**,** 151-174.

Ferrara, A., MacArthur, J. D., Wright, H. K., Modlin, I. M. & McMillen, M. A. (1990). Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *The American Journal of Surgery,* 160**,** 515-518.

Ferraro, F. J., Spillert, C. R., Swan, K. G. & Lazaro, E. J. (1992). Cold-induced hypercoagulability in vitro: A trauma connection? *American Surgeon,* 58**,** 355-357.

Filho, R. M. C., Parreira, J. G., Perlingeiro, J. A. G., Solda, S. C., de, T. & Assef, J. C. (2011). Pelvic fractures as a marker of injury severity in trauma patients

[English;Portuguese] Fratura de pelve: Um marcador de gravidade em trauma. *Revista do Colegio Brasileiro de Cirurgioes,* 38**,** 310-316.

Flin, R., Youngson, G. & Yule, S. (2007). How do surgeons make intraoperative decisions? *Quality and Safety in Health Care,* 16**,** 235-239.

Floccard, B., Rugeri, L., Faure, A., Saint, M., Boyle, E. M., Peguet, O., Levrat, A., Guillaume, C., Marcotte, G., Vulliez, A., et al. (2012). Early coagulopathy in trauma patients: an on-scene and hospital admission study. *Injury,* 43**,** 26-32.

Flor, H. (2002). Phantom-limb pain: characteristics, causes, and treatment. *Lancet Neurol,* 1**,** 182-189.

Fox, C. J., Gillespie, D. L., Cox, E. D., Kragh, J. F., Jr., Mehta, S. G., Salinas, J. & Holcomb, J. B. (2008a). Damage control resuscitation for vascular surgery in a combat support hospital. *Journal of Trauma - Injury, Infection and Critical Care,* 65**,** 1-9.

Fox, C. J., Gillespie, D. L., Cox, E. D., Mehta, S. G., Kragh, J. F., Jr., Salinas, J. & Holcomb, J. B. (2008b). The effectiveness of a damage control resuscitation strategy for vascular injury in a combat support hospital: results of a case control study. *Journal of Trauma - Injury, Infection and Critical Care,* 64**,** S99-106; discussion S106-107.

Fox, C. J., Perkins, J. G., Kragh, J. F., Jr., Singh, N. N., Patel, B. & Ficke, J. R. (2010). Popliteal artery repair in massively transfused military trauma casualties: a pursuit to save life and limb. *Journal of Trauma - Injury, Infection and Critical Care,* 69 Suppl 1**,** S123-134.

Fox, N., Rajani, R. R., Bokhari, F., Chiu, W. C., Kerwin, A., Seamon, M. J., Skarupa, D., Frykberg, E. & Eastern Association for the Surgery of, T. (2012). Evaluation and management of penetrating lower extremity arterial trauma: an Eastern Association for the Surgery of Trauma practice management guideline. *Journal of Trauma and Acute Care Surgery,* 73**,** S315-320.

Frith, D., Baptista, M. L., Cohen, M., Pearse, R., Thiemermann, C. & Brohi, K. (2011). Experimental acute traumatic coagulopathy is due to systemic activation of protein c during hypoperfusion. *Journal of Thrombosis and Haemostasis,* 9.

Frith, D., Cohen, M. J. & Brohi, K. (2012). Animal models of trauma-induced coagulopathy. *Thrombosis Research,* 129**,** 551-556.

Frith, D., Goslings, J. C., Gaarder, C., Maegele, M., Cohen, M. J., Allard, S., Johansson, P. I., Stanworth, S., Thiemermann, C. & Brohi, K. (2010). Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. *Journal of Thrombosis and Haemostasis,* 8**,** 1919-1925.

Gabbe, B. J., Simpson, P. M., Sutherland, A. M., Wolfe, R., Fitzgerald, M. C., Judson, R. & Cameron, P. A. (2012). Improved functional outcomes for major trauma patients in a regionalized, inclusive trauma system. *Annals of Surgery,* 255**,** 1009-1015.

Garg, A. X., Adhikari, N. K. J., McDonald, H., Rosas-Arellano, M. P., Devereaux, P. J., Beyene, J., Sam, J. & Haynes, R. B. (2005). Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA,* 293**,** 1223-1238.

Garrison, J. R., Richardson, J. D., Hilakos, A. S., Spain, D. A., Wilson, M. A., Miller, F. B. & Fulton, R. L. (1996). Predicting the need to pack early for severe intra-abdominal hemorrhage. *Journal of Trauma - Injury, Infection and Critical Care,* 40**,** 923-927; discussion 927-929.

Genet, G. F., Johansson, P. I., Meyer, M. A. S., Solbeck, S., Sorensen, A. M., Larsen, C. F., Welling, K. L., Windelov, N. A., Rasmussen, L. S. & Ostrowski, S. R. (2013). Trauma-induced coagulopathy: Standard coagulation tests, biomarkers of coagulopathy, and endothelial damage in patients with traumatic brain injury. *Journal of Neurotrauma,* 30**,** 301-306.

Gennarelli, T. A. W. E. A. f. t. A. o. A. M. (2008). *Abbreviated injury scale 2005 : update 2008,* Barrington, Ill., Association for the Advancement of Automative Medicine.

Georgiadis, G. M., Behrens, F. F., Joyce, M. J., Earle, A. S. & Simmons, A. L. (1993). Open tibial fractures with severe soft-tissue loss. Limb salvage compared with below-the-knee amputation. *Journal of Bone & Joint Surgery, American volume,* 75**,** 1431-1441.

Ghali, S., Harris, P. A., Khan, U., Pearse, M. & Nanchahal, J. (2005). Leg length preservation with pedicled fillet of foot flaps after traumatic amputations. *Plastic and Reconstructive Surgery,* 115**,** 498-505.

Giannoudis, P. V., Giannoudi, M. & Stavlas, P. (2009a). Damage control orthopaedics: lessons learned. *Injury,* 40**,** S47-S52.

Giannoudis, P. V., Harwood, P. J., Kontakis, G., Allami, M., Macdonald, D., Kay, S. P. & Kind, P. (2009b). Long-term quality of life in trauma patients following the full spectrum of tibial injury (fasciotomy, closed fracture, grade IIIB/IIIC open fracture and amputation). *Injury,* 40**,** 213-219.

Giannoudis, P. V., Papakostidis, C. & Roberts, C. (2006). A review of the management of open fractures of the tibia and femur. *Journal of Bone & Joint Surgery, British Volume,* 88**,** 281-289.

Gifford, S. M., Aidinian, G., Clouse, W. D., Fox, C. J., Porras, C. A., Jones, W. T., Zarzabal, L. A., Michalek, J. E., Propper, B. W. & Burkhardt, G. E. (2009). Effect of temporary shunting on extremity vascular injury: an outcome analysis from the Global War on Terror vascular injury initiative. *Journal of Vascular Surgery,* 50**,** 549-556.

Gigerenzer, G. (2002). *Reckoning with Risk: Learning to Live with Uncertainty*, Allen Lane.

Gigerenzer, G. & Edwards, A. (2003). Simple tools for understanding risks: from innumeracy to insight. *British Medical Journal,* 327**,** 741-744.

Gillespie, D. (2008). JTTS Clinical practice guidelines for vascular injury. Defense Medical Readiness Training Institute.

Glas, A. S., Lijmer, J. G., Prins, M. H., Bonsel, G. J. & Bossuyt, P. M. M. (2003). The diagnostic odds ratio: a single indicator of test performance. *Journal of Clinical Epidemiology,* 56**,** 1129-1135.

Glass, G. E., Pearse, M. F. & Nanchahal, J. (2009). Improving lower limb salvage following fractures with vascular injury: a systematic review and new management algorithm. *Journal of Plastic, Reconstructive & Aesthetic Surgery,* 62**,** 571-579.

Godina, M. (1986). Early microsurgical reconstruction of complex trauma of the extremities. *Plastic and Reconstructive Surgery,* 78**,** 285-292.

Goettler, C. E., Waibel, B. H., Goodwin, J., Watkins, F., Toschlog, E. A., Sagraves, S. G., Schenarts, P. J., Bard, M. R., Newell, M. A. & Rotondo, M. F. (2010). Trauma intensive care unit survival: how good is an educated guess? *Journal of Trauma - Injury, Infection and Critical Care,* 68**,** 1279-1288.

Gopal, S., Giannoudis, P. V., Murray, A., Matthews, S. J. & Smith, R. M. (2004). The functional outcome of severe, open tibial fractures managed with early fixation and flap coverage. *Journal of Bone & Joint Surgery, British Volume,* 86**,** 861-867.

Gopal, S., Majumder, S., Batchelor, A. G. B., Knight, S. L., De Boer, P. & Smith, R. M. (2000). Fix and flap: the radical orthopaedic and plastic treatment of severe open fractures of the tibia. *Journal of Bone & Joint Surgery, British Volume,* 82**,** 959-966.

Gordon, W. T., O'Brien, F. P., Strauss, J. E., Andersen, R. C. & Potter, B. K. (2010). Outcomes associated with the internal fixation of long-bone fractures proximal to traumatic amputations. *Journal of Bone & Joint Surgery, American volume,* 92**,** 2312-2318.

Gosselin, R. A., Roberts, I. & Gillespie, W. J. (2004). Antibiotics for preventing infection in open limb fractures. *Cochrane Database of Systematic Reviews***,** CD003764.

Gottschalk, F. (1999). Transfemoral amputation. Biomechanics and surgery. *Clinical Orthopaedics and Related Research***,** 15-22.

Greenhalgh, T. (1999). Narrative based medicine: narrative based medicine in an evidence based world. *British Medical Journal,* 318**,** 323.

Greenhalgh, T. (2014). *How to read a paper: The basics of evidence-based medicine*, Blackwell Publishing.

Greenhalgh, T., Howick, J. & Maskrey, N. (2014). Evidence based medicine: a movement in crisis? *British Medical Journal,* 348**,** g3725.

Gregory, R. T., Gould, R. J., Peclet, M., Wagner, J. S., Gilbert, D. A., Wheeler, J. R., Snyder, S. O., Gayle, R. G. & Schwab, C. W. (1985). The mangled extremity syndrome (M.E.S.): a severity grading system for multisystem injury of the extremity. *Journal of Trauma - Injury, Infection and Critical Care,* 25**,** 1147-1150.

Greuters, S., van, A. B., Franschman, G., Viersen, V. A., Beishuizen, A., Peerdeman, S. M., Boer, C. & Alarm-Bleeding, A. L. A. R. M. B. L. E. E. D. I. N. G. (2011). Acute and delayed mild coagulopathy are related to outcome in patients with isolated traumatic brain injury. *Critical Care (London, England),* 15.

Grimes, D. A. & Schulz, K. F. (2005). Surrogate end points in clinical research: hazardous to your health. *Obstetrics & Gynecology,* 105**,** 1114-1118.

Grottke, O., Braunschweig, T., Henzler, D., Coburn, M., Tolba, R. & Rossaint, R. (2010). Effects of different fibrinogen concentrations on blood loss and coagulation parameters in a pig model of coagulopathy with blunt liver injury. *Critical Care (London, England),* 14.

Gruen, R. L., Brohi, K., Schreiber, M., Balogh, Z. J., Pitt, V., Narayan, M. & Maier, R. V. (2012). Haemorrhage control in severely injured patients. *Lancet,* 380**,** 1099-1108.

Guerrero, A., Gibson, K., Kralovich, K. A., Pipinos, I., Agnostopolous, P., Carter, Y., Bulger, E., Meissner, M. & Karmy-Jones, R. (2002). Limb loss following lower extremity arterial trauma: what can be done proactively? *Injury,* 33**,** 765-769.

Gupta, R., Quinn, P., Rao, S. & Sleunarine, K. (2001). Popliteal artery trauma. A critical appraisal of an uncommon injury. *Injury,* 32**,** 357-361.

Gustilo, R. B., Mendoza, R. M. & Williams, D. N. (1984). Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. *Journal of Trauma - Injury, Infection and Critical Care,* 24**,** 742-746.

Hafez, H. M., Woolgar, J. & Robbs, J. V. (2001). Lower extremity arterial injury: results of 550 cases and review of risk factors associated with limb loss. *Journal of Vascular Surgery,* 33**,** 1212-1219.

Hanley, J. A. & McNeil, B. J. (1982). The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology,* 143**,** 29-36.

Hansen Jr, S. T. (1989). Overview of the Severely Traumatized Lower Limb Reconstruction Versus Amputation. *Clinical Orthopaedics and Related Research,* 243**,** 17-19.

Harhangi, B. S., Kompanje, E. J. O., Leebeek, F. W. G. & Maas, A. I. R. (2008). Coagulation disorders after traumatic brain injury. *Acta Neurochirurgica,* 150**,** 165-175.

Harr, J. N., Moore, E. E., Wohlauer, M. V., Droz, N., Fragoso, M., Banerjee, A. & Silliman, C. C. (2011). The acute coagulopathy of trauma is due to impaired initial thrombin generation but not clot formation or clot strength. *Journal of Surgical Research,* 170**,** 319-324.

Harris, A. M., Althausen, P. L., Kellam, J., Bosse, M. J., Castillo, R. & Lower Extremity Assessment Project Study, G. (2009). Complications following limb-threatening lower extremity trauma. *Journal of Orthopaedic Trauma,* 23**,** 1-6.

Harris, I. A., Young, J. M., Rae, H., Jalaludin, B. B. & Solomon, M. J. (2008). Predictors of general health after major trauma. *Journal of Trauma - Injury, Infection and Critical Care,* 64**,** 969-974.

Hatch, Q. M., Osterhout, L. M., Podbielski, J., Kozar, R. A., Wade, C. E., Holcomb, J. B. & Cotton, B. A. (2011). Impact of closure at the first take back: complication burden and potential overutilization of damage control laparotomy. *Journal of Trauma - Injury, Infection and Critical Care,* 71**,** 1503-1511.

Hauser, C. J., Adams, C. A., Jr. & Eachempati, S. R. (2006). Surgical Infection Society guideline: prophylactic antibiotic use in open fractures: an evidence-based guideline. *Surg Infect (Larchmt),* 7**,** 379-405.

HBS. (2013). *Harvard Business Essentials, Decision Making: 5 Steps to Better Results*, Harvard Business Review Press.

Hertel, R., Strebel, N. & Ganz, R. (1996). Amputation versus reconstruction in traumatic defects of the leg: outcome and costs. *Journal of Orthopaedic Trauma,* 10**,** 223-229.

Hess, J. R., Brohi, K., Dutton, R. P., Hauser, C. J., Holcomb, J. B., Kluger, Y., Mackway-Jones, K., Parr, M. J., Rizoli, S. B. & Yukioka, T. (2008). The coagulopathy of trauma: a review of mechanisms. *Journal of Trauma - Injury, Infection and Critical Care,* 65**,** 748-754.

Hill, A. B. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine,* 58**,** 295-300.

Hirshberg, A., Dugas, M., Banez, E. I., Scott, B. G., Wall, M. J., Mattox, K. L., Reed, R. L., Hoyt, D. B., Burris, D. & Ledgerwood, A. M. (2003). Minimizing dilutional coagulopathy in exsanguinating hemorrhage: A computer simulation. *Journal of Trauma - Injury, Infection and Critical Care,* 54**,** 454-463.

Hirshberg, A. & Mattox, K. L. (2004). *Top knife: the art & craft of trauma surgery*, TFM Publishing Limited.

Ho, A. M., Ng, C. S., Dion, P. W. & Tay, B. (2009). Computer simulation of dilutional coagulopathy. *Canadian Journal of Anesthesia,* 56.

Hoff, W. S., Bonadies, J. A., Cachecho, R. & Dorlac, W. C. (2011). East practice management guidelines work group: update to practice management guidelines for prophylactic antibiotic use in open fractures. *Journal of Trauma - Injury, Infection and Critical Care,* 70**,** 751-754.

Hoffman, M. & Monroe, D. M., 3rd (2001). A cell-based model of hemostasis. *Thrombosis and Haemostasis,* 85**,** 958-965.

Hoge, C. W., Castro, C. A., Messer, S. C., McGurk, D., Cotting, D. I. & Koffman, R. L. (2004). Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *New England Journal of Medicine,* 351**,** 13-22.

Holbrook, T. L., Anderson, J. P., Sieber, W. J., Browner, D. & Hoyt, D. B. (1999). Outcome after major trauma: 12-month and 18-month follow-up results from the Trauma Recovery Project. *Journal of Trauma - Injury, Infection and Critical Care,* 46**,** 765-771.

Holbrook, T. L. & Hoyt, D. B. (2004). The impact of major trauma: quality-of-life outcomes are worse in women than in men, independent of mechanism and injury severity. *Journal of Trauma - Injury, Infection and Critical Care,* 56**,** 284-290.

Holbrook, T. L., Hoyt, D. B. & Anderson, J. P. (2001). The importance of gender on outcome after major trauma: functional and psychologic outcomes in women versus men. *Journal of Trauma - Injury, Infection and Critical Care,* 50**,** 270-273.

Holbrook, T. L., Hoyt, D. B., Coimbra, R., Potenza, B., Sise, M. & Anderson, J. P. (2005). Long-term posttraumatic stress disorder persists after major trauma in adolescents: new data on risk factors and functional outcome. *Journal of Trauma - Injury, Infection and Critical Care,* 58**,** 764-769.

Holbrook, T. L., Hoyt, D. B., Stein, M. B. & Sieber, W. J. (2002). Gender differences in long-term posttraumatic stress disorder outcomes after major trauma: women are at higher risk of adverse outcomes than men. *Journal of Trauma - Injury, Infection and Critical Care,* 53**,** 882-888.

Holcomb, J. B., del Junco, D. J., Fox, E. E., Wade, C. E., Cohen, M. J., Schreiber, M. A., Alarcon, L. H., Bai, Y., Brasel, K. J., Bulger, E. M., et al. (2013). The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surgery,* 148**,** 127-136.

Holcomb, J. B., Jenkins, D., Rhee, P., Johannigman, J., Mahoney, P., Mehta, S., Cox, E. D., Gehrke, M. J., Beilman, G. J. & Schreiber, M. (2007a). Damage control resuscitation: directly addressing the early coagulopathy of trauma. *Journal of Trauma - Injury, Infection and Critical Care,* 62**,** 307-310.

Holcomb, J. B., McMullin, N. R., Pearse, L., Caruso, J., Wade, C. E., Oetjen-Gerdes, L., Champion, H. R., Lawnick, M., Farr, W., Rodriguez, S., et al. (2007b). Causes of death in U.S. Special Operations Forces in the global war on terrorism: 2001-2004. *Annals of Surgery,* 245**,** 986-991.

Holtslag, H. R., van Beeck, E. F., Lindeman, E. & Leenen, L. P. (2007). Determinants of long-term functional consequences after major trauma. *Journal of Trauma - Injury, Infection and Critical Care,* 62**,** 919-927.

Hoogendoorn, J. M. & van der Werken, C. (2001). Grade III open tibial fractures: functional outcome and quality of life in amputees versus patients with successful reconstruction. *Injury,* 32**,** 329-334.

Hosmer, D. W. & Lemesbow, S. (1980). Goodness of fit tests for the multiple logistic regression model. *Communications in Statistics-Theory and Methods,* 9**,** 1043-1069.

Howe, H. R., Jr., Poole, G. V., Jr., Hansen, K. J., Clark, T., Plonk, G. W., Koman, L. A. & Pennell, T. C. (1987). Salvage of lower extremities following combined orthopedic and vascular trauma. A predictive salvage index. *The American Journal of Surgery,* 53**,** 205-208.

Howick, J., Glasziou, P. & Aronson, J. K. (2009). The evolution of evidence hierarchies: what can Bradford Hill's 'guidelines for causation' contribute? *Journal of the Royal Society of Medicine,* 102**,** 186-194.

Hrafnkelsdottir, T., Erlinge, D. & Jern, S. (2001). Extracellular nucleotides ATP and UTP induce a marked acute release of tissue-type plasminogen activator in vivo in man. *Thrombosis and Haemostasis,* 85**,** 875-881.

Hubetamann, B., Lefering, R., Taeger, G., Waydhas, C., Ruchholtz, S. & Sven, D. G. U. R. (2011). Influence of prehospital fluid resuscitation on patients with multiple injuries in hemorrhagic shock in patients from the DGU trauma registry. *Journal of Emergencies, Trauma and Shock,* 4**,** 465-471.

Hughes, C. W. (1958). Arterial repair during the Korean war. *Annals of Surgery,* 147**,** 555-561.

Huse, E., Larbig, W., Flor, H. & Birbaumer, N. (2001). The effect of opioids on phantom limb pain and cortical reorganization. *Pain,* 90**,** 47-55.

Ireland, S., Endacott, R., Cameron, P., Fitzgerald, M. & Paul, E. (2011). The incidence and significance of accidental hypothermia in major trauma-A prospective observational study. *Resuscitation,* 82**,** 300-306.

Jackson, D. S. (1984). Sepsis in soft tissue limbs wounds in soldiers injured during the Falklands Campaign 1982. *Journal of the Royal Army Medical Corps,* 130**,** 97-99.

Jaeschke, R., Guyatt, G. H., Sackett, D. L., Guyatt, G., Bass, E., Brill-Edwards, P., Browman, G., Cook, D., Farkouh, M. & Gerstein, H. (1994). Users' Guides to the Medical Literature: III. How to Use an Article About a Diagnostic Test B. What Are the Results and Will They Help Me in Caring for My Patients? *JAMA,* 271**,** 703-707.

Jahangiri, M., Jayatunga, A. P., Bradley, J. W. & Dark, C. H. (1994). Prevention of phantom pain after major lower limb amputation by epidural infusion of diamorphine, clonidine and bupivacaine. *Annals of The Royal College of Surgeons of England,* 76**,** 324-326.

Jansen, J. O., Scarpelini, S., Pinto, R., Tien, H. C., Callum, J. & Rizoli, S. B. (2011). Hypoperfusion in severely injured trauma patients is associated with reduced

coagulation factor activity. *Journal of Trauma - Injury, Infection and Critical Care,* 71**,** S435-S440.

Jansen, J. O., Thomas, R., Loudon, M. A. & Brooks, A. (2009). Damage control resuscitation for patients with major trauma. *British Medical Journal,* 338**,** b1778.

Jie, Q., Yang, L., Zhu, Q., Li, M. Q., Zhao, L., Zhao, G. Y. & Hu, Y. Y. (2007). Orthopedic trauma of limbs associated with vascular injuries. *Chinese Journal of Traumatology - English Edition,* 10**,** 371-375.

Johansen, K., Daines, M., Howey, T., Helfet, D. & Hansen, S. T., Jr. (1990). Objective criteria accurately predict amputation following lower extremity trauma. *Journal of Trauma - Injury, Infection and Critical Care,* 30**,** 568-572.

Johansen, K. & Hansen Jr, S. T. (2015). MESS (Mangled Extremity Severity Score) 25 years on: Time for a reboot? *Journal of Trauma and Acute Care Surgery,* 79**,** 495-496.

Johansson, P. I., Sørensen, A. M., Larsen, C. F., Windeløv, N. A., Stensballe, J., Perner, A., Rasmussen, L. S. & Ostrowski, S. R. (2013). Low hemorrhage‐related mortality in trauma patients in a Level I trauma center employing transfusion packages and early thromboelastography‐directed hemostatic resuscitation with plasma and platelets. *Transfusion,* 53**,** 3088-3099.

Johansson, P. I., Sorensen, A. M., Perner, A., Welling, K. L., Wanscher, M., Larsen, C. F. & Ostrowski, S. R. (2011). Disseminated intravascular coagulation or acute coagulopathy of trauma shock early after trauma? An observational study. *Critical Care (London, England),* 15.

Johnson, J. L., Moore, E. E., Kashuk, J. L., Banerjee, A., Cothren, C. C., Biffl, W. L. & Sauaia, A. (2010). Effect of blood products transfusion on the development of postinjury multiple organ failure. *Archives of Surgery,* 145**,** 973-977.

Kahneman, D. (2011). *Thinking, Fast and Slow*, Farrar, Straus and Giroux.

Kaplan, E. L. & Meier, P. (1958). Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association,* 53**,** 457-481.

Kapsch, D. N., Metzler, M., Harrington, M., Mitchell, F. L. & Silver, D. (1984). Fibrinolytic response to trauma. *Surgery,* 95**,** 473-478.

Kasabian, A. K., Colen, S. R., Shaw, W. W. & Pachter, H. L. (1991). The role of microvascular free flaps in salvaging below-knee amputation stumps: a review of 22 cases. *Journal of Trauma - Injury, Infection and Critical Care,* 31**,** 495-500.

Kashuk, J. (2012). Primary fibrinolysis is intergral to the pathogenesis of the acute coagulopathy of trauma. *Shock,* 38.

Kashuk, J. L., Moore, E. E., Sawyer, M., Le, T., Johnson, J., Biffl, W. L., Cothren, C. C., Barnett, C., Stahel, P. & Sillman, C. C. (2010). Postinjury coagulopathy management: goal directed resuscitation via POC thrombelastography. *Annals of Surgery,* 251**,** 604-614.

Katz, J. & Melzack, R. (1990). Pain 'memories' in phantom limbs: review and clinical observations. *Pain,* 43**,** 319-336.

Kauvar, D. S., Sarfati, M. R. & Kraiss, L. W. (2011). National trauma databank analysis of mortality and limb loss in isolated lower extremity vascular trauma. *Journal of Vascular Surgery,* 53**,** 1598-1603.

Kawamoto, K., Houlihan, C. A., Balas, E. A. & Lobach, D. F. (2005). Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. *British Medical Journal,* 330**,** 765 - 773.

Keimowitz, R. M. & Annis, B. L. (1973). Disseminated intravascular coagulation associated with massive brain injury. *Journal of Neurosurgery,* 39**,** 178-180.

Keller, M. S., Fendya, D. G. & Weber, T. R. (2001). Glasgow Coma Scale predicts coagulopathy in pediatric trauma patients. *Seminars in Pediatric Surgery,* 10**,** 12-16.

Kelly, J. F., Ritenour, A. E., McLaughlin, D. F., Bagg, K. A., Apodaca, A. N., Mallak, C. T., Pearse, L., Lawnick, M. M., Champion, H. R., Wade, C. E., et al. (2008). Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003-2004 versus 2006. *Journal of Trauma - Injury, Infection and Critical Care,* 64**,** S21-26.

Kermode, J. C., Zheng, Q. & Milner, E. P. (1999). Marked temperature dependence of the platelet calcium signal induced by human von Willebrand factor. *Blood,* 94**,** 199-207.

Khan, S., Allard, S., Weaver, A., Barber, C., Davenport, R. & Brohi, K. (2013). A major haemorrhage protocol improves the delivery of blood component therapy and reduces waste in trauma massive transfusion. *Injury,* 44**,** 587-592.

Klein, G. A. (1993). *A recognition-primed decision (RPD) model of rapid decision making*, Ablex Publishing Corporation.

Klineberg, E. O., Crites, B. M., Flinn, W. R., Archibald, J. D. & Moorman, C. T., 3rd (2004). The role of arteriography in assessing popliteal artery injury in knee dislocations. *Journal of Trauma - Injury, Infection and Critical Care,* 56**,** 786-790.

Kohavi, R. (Year) Published. A study of cross-validation and bootstrap for accuracy estimation and model selection. 1995. 1137-1145.

Kohli, A. & Singh, G. (2008). Management of extremity vascular trauma: Jammu experience. *Asian Cardiovascular and Thoracic Annals,* 16**,** 212-214.

Konstantinidis, A., Inaba, K., Dubose, J., Barmparas, G., Lam, L., Plurad, D., Branco, B. C. & Demetriades, D. (2011). Vascular Trauma in Geriatric Patients: A National Trauma Databank Review. *The Journal of Trauma and Acute Care Surgery,* 71**,** 909-916.

Kragh, J. F., Jr., Walters, T. J., Baer, D. G., Fox, C. J., Wade, C. E., Salinas, J. & Holcomb, J. B. (2008). Practical use of emergency tourniquets to stop bleeding in major limb trauma. *Journal of Trauma - Injury, Infection and Critical Care,* 64**,** S38-49.

Kragh, J. F., Jr., Walters, T. J., Baer, D. G., Fox, C. J., Wade, C. E., Salinas, J. & Holcomb, J. B. (2009). Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Annals of Surgery,* 249**,** 1-7.

Krettek, C., Seekamp, A., Kontopp, H. & Tscherne, H. (2001). Hannover Fracture Scale '98--re-evaluation and new perspectives of an established extremity salvage score. *Injury,* 32**,** 317-328.

Krueger, C. A., Wenke, J. C. & Ficke, J. R. (2012). Ten years at war: comprehensive analysis of amputation trends. *Journal of Trauma and Acute Care Surgery,* 73**,** S438-444.

Kuralay, E., Demirkilic, U., Ozal, E., Oz, B. S., Cingoz, F., Gunay, C., Yildirim, V., Arslan, M. & Tatar, H. (2002). A quantitative approach to lower extremity vein repair. *Journal of Vascular Surgery,* 36**,** 1213-1218.

Kurtoglu, M., Yanar, H., Taviloglu, K., Sivrikoz, E., Plevin, R. & Aksoy, M. (2007). Serious lower extremity venous injury management with ligation: Prospective overview of 63 patients. *American Surgeon,* 73**,** 1039-1043.

Laferrier, J. Z. & Gailey, R. (2010). Advances in lower-limb prosthetic technology. *Physical Medicine & Rehabilitation Clinics of North America,* 21**,** 87-110.

Lange, R. H. (1989). Limb reconstruction versus amputation decision making in massive lower extremity trauma. *Clinical Orthopaedics and Related Research***,** 92-99.

Lange, R. H., Bach, A. W., Hansen, S. T., Jr. & Johansen, K. H. (1985). Open tibial fractures with associated vascular injuries: prognosis for limb salvage. *Journal of Trauma - Injury, Infection and Critical Care,* 25**,** 203-208.

Laroche, M., Kutcher, M. E., Huang, M. C., Cohen, M. J. & Manley, G. T. (2012). Coagulopathy after traumatic brain injury. *Neurosurgery,* 70**,** 1334-1345.

Lauritzen, S. L. (1995). The EM algorithm for graphical association models with missing data. *Computational Statistics & Data Analysis,* 19**,** 191-201.

Lee, S. H., Kim, K., Kim, J., Jo, Y. H., Lee, J. H., Kim, T. & Rhee, J. E. (2012). Factors associated with early coagulopathy in witnessed sudden cardiac arrest. *Critical Care Medicine,* 40.

Letson, H. L., Pecheniuk, N. M., Mhango, L. P. & Dobson, G. P. (2012). Reversal of acute coagulopathy during hypotensive resuscitation using small-volume 7.5% NaCl adenocaine and Mg2+ in the rat model of severe hemorrhagic shock. *Critical Care Medicine,* 40**,** 2417-2422.

Lewis, T., Synowiec, C., Lagomarsino, G. & Schweitzer, J. (2012). E-health in low-and middle-income countries: findings from the Center for Health Market Innovations. *Bulletin of the World Health Organization,* 90**,** 332-340.

Liu, D. S. H., Sofiadellis, F., Ashton, M., MacGill, K. & Webb, A. (2012). Early soft tissue coverage and negative pressure wound therapy optimises patient outcomes in lower limb trauma. *Injury,* 43**,** 772-778.

Liu, L., Tang, X., Pei, F. X., Tu, C. Q., Song, Y. M., Huang, F. G., Yang, T. F., Wang, G. L., Fang, Y., Zhang, H., et al. (2010). Treatment for 332 cases of lower leg fracture in "5.12" Wenchuan earthquake. *Chinese Journal of Traumatology - English Edition,* 13**,** 10-14.

Lozance, K., Dejanov, I. & Mircevski, M. (1998). Role of coagulopathy in patients with head trauma. *Journal of Clinical Neuroscience,* 5**,** 394-398.

Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., Abraham, J., Adair, T., Aggarwal, R., Ahn, S. Y., et al. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet,* 380**,** 2095-2128.

Lundborg, G. (2000). A 25-year perspective of peripheral nerve surgery: evolving neuroscientific concepts and clinical significance. *The Journal of Hand Surgery,* 25**,** 391-414.

Lustenberger, T., Talving, P., Kobayashi, L., Barmparas, G., Inaba, K., Lam, L., Branco, B. C. & Demetriades, D. (2010). Early coagulopathy after isolated severe traumatic brain injury: Relationship with hypoperfusion challenged. *Journal of Trauma - Injury, Infection and Critical Care,* 69**,** 1410-1414.

Ly, T. V., Travison, T. G., Castillo, R. C., Bosse, M. J., MacKenzie, E. J. & Group, L. S. (2008). Ability of lower-extremity injury severity scores to predict functional outcome after limb salvage. *Journal of Bone & Joint Surgery, American volume,* 90**,** 1738-1743.

Mabry, R. L., Holcomb, J. B., Baker, A. M., Cloonan, C. C., Uhorchak, J. M., Perkins, D. E., Canfield, A. J. & Hagmann, J. H. (2000). United States Army Rangers in Somalia: an analysis of combat casualties on an urban battlefield. *Journal of Trauma - Injury, Infection and Critical Care,* 49**,** 515-528.

MacKenzie, E. J. & Bosse, M. J. (2006). Factors influencing outcome following limb-threatening lower limb trauma: lessons learned from the Lower Extremity Assessment Project (LEAP). *Journal of the American Academy of Orthopaedic Surgeons,* 14**,** S205-S210.

MacKenzie, E. J., Bosse, M. J., Castillo, R. C., Smith, D. G., Webb, L. X., Kellam, J. F., Burgess, A. R., Swiontkowski, M. F., Sanders, R. W., Jones, A. L., et al. (2004). Functional outcomes following trauma-related lower-extremity amputation. *Journal of Bone & Joint Surgery, American volume,* 86-A**,** 1636-1645.

MacKenzie, E. J., Bosse, M. J., Kellam, J. F., Burgess, A. R., Webb, L. X., Swiontkowski, M. F., Sanders, R., Jones, A. L., McAndrew, M. P., Patterson, B., et al. (2002). Factors influencing the decision to amputate or reconstruct after high-energy lower extremity trauma. *Journal of Trauma - Injury, Infection and Critical Care,* 52**,** 641-649.

MacKenzie, E. J., Bosse, M. J., Kellam, J. F., Burgess, A. R., Webb, L. X., Swiontkowski, M. F., Sanders, R. W., Jones, A. L., McAndrew, M. P., Patterson, T. M., et al. (2000). Characterization of patients with high-energy lower extremity trauma. *Journal of Orthopaedic Trauma,* 14**,** 455-466.

MacKenzie, E. J., Bosse, M. J., Pollak, A. N., Webb, L. X., Swiontkowski, M. F., Kellam, J. F., Smith, D. G., Sanders, R. W., Jones, A. L., Starr, A. J., et al. (2005). Long-term persistence of disability following severe lower-limb trauma. Results of a seven-year follow-up. *Journal of Bone & Joint Surgery, American volume,* 87**,** 1801-1809.

Mackenzie, E. J., Rivara, F. P., Jurkovich, G. J., Nathens, A. B., Egleston, B. L., Salkever, D. S., Frey, K. P. & Scharfstein, D. O. (2008). The impact of trauma-center care on functional outcomes following major lower-limb trauma. *Journal of Bone & Joint Surgery, American volume,* 90**,** 101-109.

MacKenzie, E. J., Rivara, F. P., Jurkovich, G. J., Nathens, A. B., Frey, K. P., Egleston, B. L., Salkever, D. S. & Scharfstein, D. O. (2006). A national evaluation of the effect of trauma-center care on mortality. *New England Journal of Medicine,* 354**,** 366-378.

MacLennan, S. & Williamson, L. M. (2006). Risks of fresh frozen plasma and platelets. *Journal of Trauma - Injury, Infection and Critical Care,* 60**,** S46-S50.

Maegele, M., Lefering, R., Yucel, N., Tjardes, T., Rixen, D., Paffrath, T., Simanski, C., Neugebauer, E. & Bouillon, B. (2007). Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. *Injury,* 38**,** 298-304.

Makitie, I., Mattila, V. M. & Pihlajamaki, H. (2006). Severe vascular gunshot injuries of the extremities: A ten-year nation-wide analysis from Finland. *Scandinavian Journal of Surgery,* 95**,** 49-54.

Malone, D. L., Dunne, J., Tracy, J. K., Putnam, A. T., Scalea, T. M. & Napolitano, L. M. (2003). Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *Journal of Trauma - Injury, Infection and Critical Care,* 54**,** 898-907.

Malone, D. L., Hess, J. R. & Fingerhut, A. (2006). Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. *Journal of Trauma - Injury, Infection and Critical Care,* 60**,** S91-S96.

Mannion, S. J. & Chaloner, E. (2005). Principles of war surgery. *British Medical Journal,* 330**,** 1498-1500.

Marks, L. J. & Michael, J. W. (2001). Science, medicine, and the future: Artificial limbs. *British Medical Journal,* 323**,** 732-735.

Martin, R. S., Kilgo, P. D., Miller, P. R., Hoth, J. J., Meredith, J. W. & Chang, M. C. (2005). Injury-associated hypothermia: an analysis of the 2004 National Trauma Data Bank. *Shock,* 24**,** 114-118.

Martini, W. Z., Chinkes, D. L., Pusateri, A. E., Holcomb, J. B., Yu, Y. M., Zhang, X. J. & Wolfe, R. R. (2005a). Acute changes in fibrinogen metabolism and coagulation after hemorrhage in pigs. *American Journal of Physiology - Endocrinology and Metabolism,* 289**,** E930-E934.

Martini, W. Z., Cortez, D. S., Dubick, M. A., Park, M. S. & Holcomb, J. B. (2008). Thrombelastography is better than PT, aPTT, and activated clotting time in detecting clinically relevant clotting abnormalities after hypothermia, hemorrhagic shock and resuscitation in pigs. *Journal of Trauma - Injury, Infection and Critical Care,* 65**,** 535-543.

Martini, W. Z., Dubick, M. A., Pusateri, A. E., Park, M. S., Ryan, K. L. & Holcomb, J. B. (2006). Does bicarbonate correct coagulation function impaired by acidosis in swine? *Journal of Trauma - Injury, Infection and Critical Care,* 61**,** 99-106.

Martini, W. Z., Dubick, M. A., Wade, C. E. & Holcomb, J. B. (2007). Evaluation of tris-hydroxymethylaminomethane on reversing coagulation abnormalities caused by acidosis in pigs. *Critical Care Medicine,* 35**,** 1568-1574.

Martini, W. Z., Pusateri, A. E., Uscilowicz, J. M., Delgado, A. V., Holcomb, J. B., Tyburski, J. G., Rhee, P. M. & Schreiber, M. A. (2005b). Independent contributions of

hypothermia and acidosis to coagulopathy in swine. *Journal of Trauma - Injury, Infection and Critical Care,* 58**,** 1002-1010.

McCarthy, M. L., MacKenzie, E. J., Edwin, D., Bosse, M. J., Castillo, R. C., Starr, A. & group, L. s. (2003). Psychological distress associated with severe lower-limb injury. *Journal of Bone & Joint Surgery, American volume,* 85**,** 1689-1697.

McHenry, T. P., Holcomb, J. B., Aoki, N. & Lindsey, R. W. (2002). Fractures with major vascular injuries from gunshot wounds: implications of surgical sequence. *Journal of Trauma - Injury, Infection and Critical Care,* 53**,** 717-721.

McNamara, M. G., Heckman, J. D. & Corley, F. G. (1994). Severe open fractures of the lower extremity: a retrospective evaluation of the Mangled Extremity Severity Score (MESS). *Journal of Orthopaedic Trauma,* 8**,** 81-87.

Meng, Z. H., Wolberg, A. S., Monroe, D. M., 3rd & Hoffman, M. (2003). The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. *Journal of Trauma - Injury, Infection and Critical Care,* 55**,** 886-891.

Michelson, A. D., MacGregor, H., Barnard, M. R., Kestin, A. S., Rohrer, M. J. & Valeri, C. R. (1994). Reversible inhibition of human platelet activation by hypothermia in vivo and in vitro. *Thrombosis and Haemostasis,* 71**,** 633-640.

Miller, R. S., Morris Jr, J. A., Diaz Jr, J. J., Herring, M. B. & May, A. K. (2005). Complications after 344 damage-control open celiotomies. *Journal of Trauma - Injury, Infection and Critical Care,* 59**,** 1365-1374.

Mills, W. J., Barei, D. P. & McNair, P. (2004). The value of the ankle-brachial index for diagnosing arterial injury after knee dislocation: A prospective study. *Journal of Trauma - Injury, Infection and Critical Care,* 56**,** 1261-1265.

Miranda, F. E., Dennis, J. W., Veldenz, H. C., Dovgan, P. S. & Frykberg, E. R. (2002). Confirmation of the safety and accuracy of physical examination in the evaluation of

knee dislocation for injury of the popliteal artery: a prospective study. *Journal of Trauma - Injury, Infection and Critical Care,* 52**,** 247-251.

Misra, A. & Nanchahal, J. (2003). Use of gauze soaked in povidone iodine for dressing acute open wounds. *Plastic and Reconstructive Surgery,* 111**,** 2105-2107.

Mitchell Iii, F. L. & Thal, E. R. (1990). Results of venous interposition grafts in arterial injuries. *Journal of Trauma - Injury, Infection and Critical Care,* 30**,** 336-339.

Mitra, B., Cameron, P. A. & Gruen, R. L. (2012a). Aggressive fresh frozen plasma (FFP) with massive blood transfusion in the absence of acute traumatic coagulopathy. *Injury,* 43**,** 33-37.

Mitra, B., Cameron, P. A., Mori, A., Maini, A., Fitzgerald, M., Paul, E. & Street, A. (2011). Early prediction of acute traumatic coagulopathy. *Resuscitation,* 82**,** 1208-1213.

Mitra, B., O'Reilly, G., Collecutt, M., Cameron, P. A., Phillips, L. & Davis, A. (2012b). Prospective comparison of point-of-care international normalised ratio measurement versus plasma international normalised ratio for acute traumatic coagulopathy. *Emergency Medicine Australasia,* 24**,** 363-368.

Mitrophanov, A. Y., Rosendaal, F. R. & Reifman, J. (2013). Computational analysis of the effects of reduced temperature on thrombin generation: The contributions of hypothermia to coagulopathy. *Anesthesia and Analgesia,* 117**,** 565-574.

Mkandawire, N. C., Boot, D. A., Braithwaite, I. J. & Patterson, M. (2002). Musculoskeletal recovery 5 years after severe injury: long term problems are common. *Injury,* 33**,** 111-115.

Mock, C. & Cherian, M. N. (2008). The global burden of musculoskeletal injuries: challenges and solutions. *Clinical Orthopaedics and Related Research,* 466**,** 2306-2316.

Mock, C., MacKenzie, E., Jurkovich, G., Burgess, A., Cushing, B., deLateur, B., McAndrew, M., Morris, J. & Swiontkowski, M. (2000). Determinants of disability after

lower extremity fracture. *Journal of Trauma - Injury, Infection and Critical Care,* 49**,** 1002-1011.

Mock, C. N., Boland, E., Acheampong, F. & Adjei, S. (2003). Long-term injury related disability in Ghana. *Disability and Rehabilitation,* 25**,** 732-741.

Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal,* 339**,** b2535.

Mohr, J., Ruchholtz, S., Hildebrand, F., Flohe, S., Frink, M., Witte, I., Weuster, M., Frohlich, M., Van, M., Keibl, C., et al. (2013). Induced hypothermia does not impair coagulation system in a swine multiple trauma model. *Journal of Trauma and Acute Care Surgery,* 74**,** 1014-1020.

Moini, M., Takyar, M. A. & Rasouli, M. R. (2007). Revascularisation later than 24h after popliteal artery trauma: is it worthwhile? *Injury,* 38**,** 1098-1101.

Moons, K. G. M., Royston, P., Vergouwe, Y., Grobbee, D. E. & Altman, D. G. (2009). Prognosis and prognostic research: what, why, and how? *British Medical Journal,* 338**,** 1317 - 1320.

Moues, C. M., Vos, M. C., van den Bemd, G. J., Stijnen, T. & Hovius, S. E. (2004). Bacterial load in relation to vacuum-assisted closure wound therapy: a prospective randomized trial. *Wound Repair and Regeneration,* 12**,** 11-17.

Mullenix, P. S., Steele, S. R., Andersen, C. A., Starnes, B. W., Salim, A. & Martin, M. J. (2006). Limb salvage and outcomes among patients with traumatic popliteal vascular injury: an analysis of the National Trauma Data Bank. *Journal of Vascular Surgery,* 44**,** 94-100.

Murray, C. J., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J. A., Abdalla, S., et al. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet,* 380**,** 2197-2223.

Murray, C. K., Hsu, J. R., Solomkin, J. S., Keeling, J. J., Andersen, R. C., Ficke, J. R. & Calhoun, J. H. (2008). Prevention and management of infections associated with combat-related extremity injuries. *Journal of Trauma - Injury, Infection and Critical Care,* 64**,** S239-251.

Naique, S. B., Pearse, M. & Nanchahal, J. (2006). Management of severe open tibial fractures: the need for combined orthopaedic and plastic surgical treatment in specialist centres. *Journal of Bone & Joint Surgery, British Volume,* 88**,** 351-357.

Nair, R., Abdool-Carrim, A. T. & Robbs, J. V. (2000). Gunshot injuries of the popliteal artery. *British Journal of Surgery,* 87**,** 602-607.

Nanchahal J, N. D., Khan U, Moran C, Barrett S, Sanderson F, Pallister I. (2009). *Standards for the management of open fractures of the lower limb,* London, Royal Society of Medicine Press.

Nardai, G., Gombkoto, A., Basta, M., Rosivall, L. & Szebeni, J. (2009). Associations between complement system activation and acute traumatic coagulopathy. *European Journal of Anaesthesiology,* 26.

Nayagam, S., Graham, K., Pearse, M. & Nanchahal, J. (2011). Reconstructive surgery in limbs: the case for the orthoplastic approach. *Annals of Plastic Surgery,* 66**,** 6-8.

Neil, M., Tailor, M. & Marquez, D. (2007). Inference in hybrid Bayesian networks using dynamic discretization. *Statistics and Computing,* 17**,** 219-233.

Nicandri, G. T., Dunbar, R. P. & Wahl, C. J. (2010). Are evidence-based protocols which identify vascular injury associated with knee dislocation underutilized? *Knee Surgery, Sports Traumatology, Arthroscopy,* 18**,** 1005-1012.

NICE. (2016). Major trauma: Complex fractures. *NICE guideline.* National Institute for Health and Care Excellence.

Nikolajsen, L., Hansen, C. L., Nielsen, J., Keller, J., Arendt-Nielsen, L. & Jensen, T. S. (1996). The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. *Pain,* 67**,** 69-77.

Nikolajsen, L. & Jensen, T. S. (2001). Phantom limb pain. *British Journal of Anaesthesia,* 87**,** 107-116.

Nikoli, D. K., Jovanovi, Z., Turkovi, G., Vulovi, R. & Mladenovi, M. (2002). Supracondylar missile fractures of the femur. *Injury,* 33**,** 161-166.

Niles, S. E., McLaughlin, D. F., Perkins, J. G., Wade, C. E., Li, Y., Spinella, P. C. & Holcomb, J. B. (2008). Increased mortality associated with the early coagulopathy of trauma in combat casualties. *Journal of Trauma - Injury, Infection and Critical Care,* 64**,** 1459-1463.

OED. (2015). "viability, n.". *Oxford English Dictionary.* Oxford: Oxford University Press.

Ofri, D. (2013). Uncertainty is hard for doctors. *New York Times*, June 6, 2013.

Ogweno, G. O. & Gwer, S. (2013). Haemodilution with Nacl solutions below 600mOsm/L Induce hypercoagulability while concentrations above 1200 mOsm/L progressively impair coagulation as evaluated with thrombelastography in vitro. *Journal of Thrombosis and Haemostasis,* 11**,** 1028-1029.

Orgill, D. P. & Bayer, L. R. (2011). Update on negative-pressure wound therapy. *Plastic and Reconstructive Surgery,* 127 Suppl 1**,** 105S-115S.

Owens, B. D., Kragh, J. F., Jr., Macaitis, J., Svoboda, S. J. & Wenke, J. C. (2007). Characterization of extremity wounds in Operation Iraqi Freedom and Operation Enduring Freedom. *Journal of Orthopaedic Trauma,* 21**,** 254-257.

Owens, B. D., Kragh, J. F., Jr., Wenke, J. C., Macaitis, J., Wade, C. E. & Holcomb, J. B. (2008). Combat wounds in operation Iraqi Freedom and operation Enduring Freedom. *Journal of Trauma - Injury, Infection and Critical Care,* 64**,** 295-299.

Padberg, F. T., Rubelowsky, J. J., Hernandez-Maldonado, J. J., Milazzo, V., Swan, K. G., Lee, B. C. & Hobson, R. W. (1992). Infrapopliteal arterial injury: prompt revascularization affords optimal limb salvage. *Journal of Vascular Surgery,* 16**,** 877-886.

Pape, H. C. (2008). Effects of changing strategies of fracture fixation on immunologic changes and systemic complications after multiple trauma: damage control orthopedic surgery. *Journal of Orthopaedic Research,* 26**,** 1478-1484.

Pape, H. C., Probst, C., Lohse, R., Zelle, B. A., Panzica, M., Stalp, M., Steel, J. L., Duhme, H. M., Pfeifer, R., Krettek, C., et al. (2010). Predictors of late clinical outcome following orthopedic injuries after multiple trauma. *Journal of Trauma - Injury, Infection and Critical Care,* 69**,** 1243-1251.

Park, K. H., Lee, K. H. & Kim, H. (2013). Effect of hypothermia on coagulatory function and survival in Sprague-Dawley rats exposed to uncontrolled haemorrhagic shock. *Injury,* 44**,** 91-96.

Park, S. H., Silva, M., Bahk, W. J., McKellop, H. & Lieberman, J. R. (2002). Effect of repeated irrigation and debridement on fracture healing in an animal model. *Journal of Orthopaedic Research,* 20**,** 1197-1204.

Parmaksizoglu, F., Koprulu, A. S., Unal, M. B. & Cansu, E. (2010). Early or delayed limb lengthening after acute shortening in the treatment of traumatic below-knee amputations and Gustilo and Anderson type IIIC open tibial fractures: The results of a case series. *Journal of Bone & Joint Surgery, British Volume,* 92**,** 1563-1567.

Patterson, B. M., Agel, J., Swiontkowski, M. F., MacKenzie, E. J., Bosse, M. J., Kellam, J. F., Burgess, A. R., Webb, L. X., Sanders, R. W., Jones, A. L., et al. (2007). Knee dislocations with vascular injury: Outcomes in the Lower Extremity Assessment Project (LEAP) study. *Journal of Trauma - Injury, Infection and Critical Care,* 63**,** 855-858.

Patzakis, M. J. & Wilkins, J. (1989). Factors influencing infection rate in open fracture wounds. *Clinical Orthopaedics and Related Research*, 36-40.

Pauley, K., Flin, R., Yule, S. & Youngson, G. (2011). Surgeons' intraoperative decision making and risk management. *The American Journal of Surgery,* 202, 375-381.

Peduzzi, P., Concato, J., Feinstein, A. R. & Holford, T. R. (1995). Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates. *Journal of Clinical Epidemiology,* 48, 1503-1510.

Peiniger, S., Nienaber, U., Lefering, R., Braun, M., Wafaisade, A., Borgman, M. A., Spinella, P. C. & Maegele, M. (2012). Glasgow Coma Scale as a predictor for hemocoagulative disorders after blunt pediatric traumatic brain injury*. *Pediatric Critical Care Medicine,* 13, 455-460.

Percival, T. J. & Rasmussen, T. E. (2012). Reperfusion strategies in the management of extremity vascular injury with ischaemia. *British Journal of Surgery,* 99, 66-74.

Perkins, Z. B., De'ath, H. D., Aylwin, C., Brohi, K., Walsh, M. & Tai, N. R. (2012). Epidemiology and outcome of vascular trauma at a british major trauma centre. *European Journal of Vascular and Endovascular Surgery,* 44, 203-209.

Perkins, Z. B., Maytham, G. D., Koers, L., Bates, P., Brohi, K. & Tai, N. R. (2014). Impact on outcome of a targeted performance improvement programme in haemodynamically unstable patients with a pelvic fracture. *The Bone and Joint Journal,* 96-B, 1090-1097.

Perkins, Z. B., Yet, B., Glasgow, S., Cole, E., Marsh, W., Brohi, K., Rasmussen, T. E. & Tai, N. R. (2015). Meta-analysis of prognostic factors for amputation following surgical repair of lower extremity vascular trauma. *British Journal of Surgery,* 102, 436-450.

Persson, B. (2001). Lower limb amputation. Part 1: Amputation methods--a 10 year literature review. *Prosthetics and Orthotics International,* 25, 7-13.

Pinzur, M. S., Beck, J., Himes, R. & Callaci, J. (2008). Distal tibiofibular bone-bridging in transtibial amputation. *Journal of Bone & Joint Surgery, American volume,* 90**,** 2682-2687.

Pinzur, M. S., Gottschalk, F. A., Pinto, M. A. & Smith, D. G. (2007). Controversies in lower-extremity amputation. *Journal of Bone & Joint Surgery, American volume,* 89**,** 1118-1127.

Pinzur, M. S., Pinto, M. A., Saltzman, M., Batista, F., Gottschalk, F. & Juknelis, D. (2006). Health-related quality of life in patients with transtibial amputation and reconstruction with bone bridging of the distal tibia and fibula. *Foot & Ankle International,* 27**,** 907-912.

Polinder, S., van Beeck, E. F., Essink-Bot, M. L., Toet, H., Looman, C. W., Mulder, S. & Meerding, W. J. (2007). Functional outcome at 2.5, 5, 9, and 24 months after injury in the Netherlands. *Journal of Trauma - Injury, Infection and Critical Care,* 62**,** 133-141.

Pollak, A. N., Jones, A. L., Castillo, R. C., Bosse, M. J. & MacKenzie, E. J. (2010). The relationship between time to surgical debridement and incidence of infection after open high-energy lower extremity trauma. *Journal of Bone & Joint Surgery, American volume,* 92**,** 7-15.

Pommerening, M. J., Goodman, M. D., Holcomb, J. B., Wade, C. E., Fox, E. E., del Junco, D. J., Brasel, K. J., Bulger, E. M., Cohen, M. J. & Alarcon, L. H. (2015). Clinical gestalt and the prediction of massive transfusion after trauma. *Injury,* 46**,** 807-813.

Poole, G. V., Ward, E. F., Griswold, J. A., Muakkassa, F. F. & Hsu, H. S. (1992). Complications of pelvic fractures from blunt trauma. *American Surgeon,* 58**,** 225-231.

Porter, K. M. (2010). Prehospital amputation. *Emergency Medicine Journal,* 27**,** 940-942.

Pourzand, A., Fakhri, B. A., Azhough, R., Hassanzadeh, M. A., Hashemzadeh, S. & Bayat, A. M. (2010). Management of high-risk popliteal vascular blunt trauma: clinical experience with 62 cases. *Vascular Health and Risk Management,* 6**,** 613-618.

Pozo, J. L., Powell, B., Andrews, B. G., Hutton, P. A. & Clarke, J. (1990). The timing of amputation for lower limb trauma. *Journal of Bone & Joint Surgery, British Volume,* 72**,** 288-292.

Prantl, L., Schreml, S., Heine, N., Eisenmann-Klein, M. & Angele, P. (2006). Surgical treatment of chronic phantom limb sensation and limb pain after lower limb amputation. *Plastic and Reconstructive Surgery,* 118**,** 1562-1572.

Rabin, R. & Charro, F. d. (2001). EQ-SD: a measure of health status from the EuroQol Group. *Annals of Medicine,* 33**,** 337-343.

Rajasekaran, S., Naresh Babu, J., Dheenadhayalan, J., Shetty, A. P., Sundararajan, S. R., Kumar, M. & Rajasabapathy, S. (2006). A score for predicting salvage and outcome in Gustilo type-IIIA and type-IIIB open tibial fractures. *Journal of Bone & Joint Surgery, British Volume,* 88**,** 1351-1360.

Rasmussen, T. E., Clouse, W. D., Jenkins, D. H., Peck, M. A., Eliason, J. L. & Smith, D. L. (2006a). Echelons of care and the management of wartime vascular injury: a report from the 332nd EMDG/Air Force Theater Hospital, Balad Air Base, Iraq. *Perspectives in Vascular Surgery and Endovascular Therapy,* 18**,** 91-99.

Rasmussen, T. E., Clouse, W. D., Jenkins, D. H., Peck, M. A., Eliason, J. L. & Smith, D. L. (2006b). The use of temporary vascular shunts as a damage control adjunct in the management of wartime vascular injury. *Journal of Trauma - Injury, Infection and Critical Care,* 61**,** 8-15.

Raza, I., Davenport, R., Rourke, C., Platton, S., Manson, J., Spoors, C., Khan, S., De'Ath, H. D., Allard, S., Hart, D. P., et al. (2013). The incidence and magnitude of fibrinolytic activation in trauma patients. *Journal of Thrombosis and Haemostasis,* 11**,** 307-314.

Rich, N. M., Baugh, J. H. & Hughes, C. W. (1970). Acute arterial injuries in Vietnam: 1,000 cases. *Journal of Trauma - Injury, Infection and Critical Care,* 10**,** 359-369.

Ringburg, A. N., Polinder, S., van Ierland, M. C., Steyerberg, E. W., van Lieshout, E. M., Patka, P., van Beeck, E. F. & Schipper, I. B. (2011). Prevalence and prognostic factors

of disability after major trauma. *Journal of Trauma - Injury, Infection and Critical Care,* 70**,** 916-922.

Rivara, F. P., Mackenzie, E. J., Jurkovich, G. J., Nathens, A. B., Wang, J. & Scharfstein, D. O. (2008). Prevalence of pain in patients 1 year after major trauma. *Archives of Surgery,* 143**,** 282-287.

Roberts, D. J., Bobrovitz, N., Zygun, D. A., Ball, C. G., Kirkpatrick, A. W., Faris, P. D. & Stelfox, H. T. (2015). Indications for use of damage control surgery and damage control interventions in civilian trauma patients: A scoping review. *Journal of Trauma and Acute Care Surgery,* 78**,** 1187-1196.

Roberts, I., Shakur, H., Afolabi, A., Brohi, K., Coats, T., Dewan, Y., Gando, S., Guyatt, G., Hunt, B. J., Morales, C., et al. (2011). The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet,* 377**,** 1096-1101.

Robertson, P. A. (1991). Prediction of amputation after severe lower limb trauma. *Journal of Bone & Joint Surgery, British Volume,* 73**,** 816-818.

Rosenfeld, J. V., Maas, A. I., Bragge, P., Morganti-Kossmann, M. C., Manley, G. T. & Gruen, R. L. (2012). Early management of severe traumatic brain injury. *Lancet,* 380**,** 1088-1098.

Rossaint, R., Bouillon, B., Cerny, V., Coats, T. J., Duranteau, J., Fernandez-Mondejar, E., Hunt, B. J., Komadina, R., Nardi, G., Neugebauer, E., et al. (2010). Management of bleeding following major trauma: an updated European guideline. *Critical Care (London, England),* 14**,** R52.

Rotondo, M. F., Schwab, C. W., McGonigal, M. D., Phillips, G. R., Fruchterman, T. M., Kauder, D. R., Latenser, B. A. & Angood, P. A. (1993). 'Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. *Journal of Trauma - Injury, Infection and Critical Care,* 35**,** 375-383.

Rourke, C., Curry, N. S., Khan, S., Stanworth, S. & Brohi, K. (2011). Characterization of fibrinogen depletion and response to replacement therapy in bleeding trauma patients. *Journal of Thrombosis and Haemostasis,* 9.

Rousseau, R., Tremblay, S. & Breton, R. (2004). Defining and Modeling Situation Awareness: a Critical Review. *In:* Banbury, S. & Tremblay, S. (eds.) *A Cognitive Approach to Situation Awareness: Theory and Application.* Ashgate Publishing Limited.

Royston, P., Moons, K. G. M., Altman, D. G. & Vergouwe, Y. (2009). Prognosis and prognostic research: developing a prognostic model. *British Medical Journal,* 338**,** b604.

Rozycki, G. S., Tremblay, L. N., Feliciano, D. V. & McClelland, W. B. (2003). Blunt vascular trauma in the extremity: diagnosis, management, and outcome. *Journal of Trauma - Injury, Infection and Critical Care,* 55**,** 814-825.

Rugeri, L., Levrat, A., David, J. S., Delecroix, E., Floccard, B., Gros, A., Allaouchiche, B. & Negrier, C. (2007). Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. *Journal of Thrombosis and Haemostasis,* 5**,** 289-295.

Russell, W. L., Sailors, D. M., Whittle, T. B., Fisher, D. F., Jr. & Burns, R. P. (1991). Limb salvage versus traumatic amputation. A decision based on a seven-part predictive index. *Annals of Surgery,* 213**,** 473-480.

Sackett, D. L., Rosenberg, W. M., Gray, J. A., Haynes, R. B. & Richardson, W. S. (1996). Evidence based medicine: what it is and what it isn't. *British Medical Journal,* 312**,** 71.

Sagraves, S. G., Conquest, A. M., Albrecht, R. J., Toschlog, E. A., Schenarts, P. J., Bard, M. R., Powell, C. S. & Rotondo, M. F. (2003). Popliteal artery trauma in a rural level I trauma center. *American Surgeon,* 69**,** 485-489.

Sasser, S. M., Hunt, R. C., Faul, M., Sugerman, D., Pearson, W. S., Dulski, T., Wald, M. M., Jurkovich, G. J., Newgard, C. D. & Lerner, E. B. (2012). Guidelines for field triage of injured patients: recommendations of the National Expert Panel on Field Triage, 2011. *MMWR. Recommendations and reports: Morbidity and mortality weekly report. Recommendations and reports/Centers for Disease Control,* 61**,** 1-20.

Scalea, T. M., Boswell, S. A., Scott, J. D., Mitchell, K. A., Kramer, M. E. & Pollak, A. N. (2000). External fixation as a bridge to intramedullary nailing for patients with multiple injuries and with femur fractures: damage control orthopedics. *Journal of Trauma - Injury, Infection and Critical Care,* 48**,** 613-623.

Scalea, T. M., DuBose, J., Moore, E. E., West, M., Moore, F. A., McIntyre, R., Cocanour, C., Davis, J., Ochsner, M. G. & Feliciano, D. (2012). Western Trauma Association critical decisions in trauma: management of the mangled extremity. *Journal of Trauma and Acute Care Surgery,* 72**,** 86-93.

Schreiber, M. A. (2012). The beginning of the end for damage control surgery. *British Journal of Surgery,* 99**,** 10-11.

Schreiber, M. A., Perkins, J., Kiraly, L., Underwood, S., Wade, C. & Holcomb, J. B. (2007). Early predictors of massive transfusion in combat casualties. *Journal of the American College of Surgeons,* 205**,** 541-545.

Scott, B. G. & Hirshberg, A. (2004). Exclusion and bypass--a new approach to popliteal artery injuries. *Journal of Trauma - Injury, Infection and Critical Care,* 57**,** 913-914.

Scott, J. & Huskisson, E. C. (1976). Graphic representation of pain. *Pain,* 2**,** 175-184.

Seddon, H. J. (1943). Three types of nerve injury. *Brain,* 66**,** 237-288.

Shackford, S. R., Kahl, J. E., Calvo, R. Y., Shackford, M. C., Danos, L. A., Davis, J. W., Vercruysse, G. A., Feliciano, D. V., Moore, E. E. & Moore, H. B. (2013). Limb salvage after complex repairs of extremity arterial injuries is independent of surgical specialty training. *Journal of Trauma and Acute Care Surgery,* 74**,** 716-724.

Shapiro, M. B., Jenkins, D. H., Schwab, C. W. & Rotondo, M. F. (2000). Damage control: collective review. *Journal of Trauma - Injury, Infection and Critical Care,* 49**,** 969-978.

Shaz, B. H., Winkler, A. M., James, A. B., Hillyer, C. D. & MacLeod, J. B. (2011). Pathophysiology of early trauma-induced coagulopathy: Emerging evidence for hemodilution and coagulation factor depletion. *Journal of Trauma - Injury, Infection and Critical Care,* 70**,** 1401-1406.

Shcherbina, I. A., Lipets, E. N., Balandina, A. N. & Ataullakhanov, F. I. (2013). Influence of temperature on fibrin clot formation process in thrombodynamics and routine clotting tests. *Journal of Thrombosis and Haemostasis,* 11.

Sheean, A. J., Krueger, C. A., Napierala, M. A., Stinner, D. J., Hsu, J. R., Skeletal, T. & Research, C. (2014). Evaluation of the mangled extremity severity score in combat-related type III open tibia fracture. *Journal of Orthopaedic Trauma,* 28**,** 523-526.

Sherren, P., Hussey, J., Martin, R., Kundishora, T., Parker, M. & Emerson, B. (2013). Acute burn induced coagulopathy. *Burns,* 39**,** 1157-1161.

Shih, R. A., Schell, T. L., Hambarsoomian, K., Belzberg, H. & Marshall, G. N. (2010). Prevalence of posttraumatic stress disorder and major depression after trauma center hospitalization. *Journal of Trauma - Injury, Infection and Critical Care,* 69**,** 1560-1566.

Simmons, J. D., Duchesne, J. C., Ahmed, N., Schmieg, R. E., Jr., Rushton, F. W., Porter, J. M. & Mitchell, M. E. (2012). The weight of obesity in patients with lower extremity vascular injuries. *Injury,* 43**,** 582-584.

Simmons, J. W., White, C. E., Ritchie, J. D., Hardin, M. O., Dubick, M. A. & Blackbourne, L. H. (2011). Mechanism of injury affects acute coagulopathy of trauma in combat casualties. *Journal of Trauma - Injury, Infection and Critical Care,* 71**,** S74-S77.

Sixta, S. L., Hatch, Q. M., Matijevic, N., Wade, C. E., Holcomb, J. B. & Cotton, B. A. (2012). Mechanistic determinates of the acute coagulopathy of trauma (ACoT) in

patients requiring emergency surgery. *International Journal of Burns & Trauma,* 2**,** 158-166.

Smith, D. G. & Fergason, J. R. (1999). Transtibial amputations. *Clinical Orthopaedics and Related Research***,** 108-115.

Smith, J., Greaves, I. & Porter, K. (2010). The trauma epidemic. *Oxford Desk Reference-Major Trauma.* Oxford University Press.

Soni, A., Tzafetta, K., Knight, S. & Giannoudis, P. V. (2012). Gustilo IIIC fractures in the lower limb: our 15-year experience. *Journal of Bone & Joint Surgery, British Volume,* 94**,** 698-703.

Sorensen, B. & Fries, D. (2012). Emerging treatment strategies for trauma-induced coagulopathy. *British Journal of Surgery,* 99 Suppl 1**,** 40-50.

Sox, H. C., Higgins, M. C. & Owens, D. K. (2013). *Medical Decision Making*, Wiley-Blackwell.

Spahn, D. R., Bouillon, B., Cerny, V., Coats, T. J., Duranteau, J., Fernandez-Mondejar, E., Filipescu, D., Hunt, B. J., Komadina, R., Nardi, G., et al. (2013). Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Critical Care (London, England),* 17**,** R76.

Spicer, C. C. (1980). Test reduction: II--Bayes's theorem and the evaluation of tests. *British Medical Journal,* 281**,** 592-594.

Spinner, R. J. & Kline, D. G. (2000). Surgery for peripheral nerve and brachial plexus injuries or other nerve lesions. *Muscle & Nerve,* 23**,** 680-695.

Sriussadaporn, S. & Pak-art, R. (2002). Temporary intravascular shunt in complex extremity vascular injuries. *Journal of Trauma - Injury, Infection and Critical Care,* 52**,** 1129-1134.

Stannard, A., Scott, D. J., Ivatury, R. A., Miller, D. L., Ames-Chase, A. C., Feider, L. L., Porras, C. A., Gifford, S. M. & Rasmussen, T. E. (2012). A collaborative research system for functional outcomes following wartime extremity vascular injury. *Journal of Trauma and Acute Care Surgery,* 73**,** S7-12.

Stannard, J. P., Volgas, D. A., Stewart, R., McGwin, G., Jr. & Alonso, J. E. (2009). Negative pressure wound therapy after severe open fractures: a prospective randomized study. *Journal of Orthopaedic Trauma,* 23**,** 552-557.

Stansbury, L. G., Lalliss, S. J., Branstetter, J. G., Bagg, M. R. & Holcomb, J. B. (2008). Amputations in U.S. military personnel in the current conflicts in Afghanistan and Iraq. *Journal of Orthopaedic Trauma,* 22**,** 43-46.

Stanworth, S. J., Morris, T. P., Gaarder, C., Goslings, J. C., Maegele, M., Cohen, M. J., König, T. C., Davenport, R. A., Pittet, J.-F. & Johansson, P. I. (2010). Reappraising the concept of massive transfusion in trauma. *Critical Care (London, England),* 14**,** R239.

Steyerberg, E. W. (2008). Overfitting and Optimism in Prediction Models. *Clinical prediction models: a practical approach to development, validation, and updating.* Springer Science & Business Media.

Steyerberg, E. W., Eijkemans, M. J., Harrell, F. E., Jr. & Habbema, J. D. (2001). Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. *Medical Decision Making,* 21**,** 45-56.

Steyerberg, E. W., Moons, K. G., van der Windt, D. A., Hayden, J. A., Perel, P., Schroter, S., Riley, R. D., Hemingway, H., Altman, D. G. & Group, P. (2013). Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med,* 10**,** e1001381.

Stone, H. H., Strom, P. R. & Mullins, R. J. (1983). Management of the major coagulopathy with onset during laparotomy. *Annals of Surgery,* 197**,** 532.

Subasi, M., Cakir, O., Kesemenli, C., Arslan, H., Necmioglu, S. & Eren, N. (2001). Popliteal artery injuries associated with fractures and dislocations about the knee. *Acta Orthopaedica Belgica,* 67**,** 259-266.

Subramanian, A., Vercruysse, G., Dente, C., Wyrzykowski, A., King, E. & Feliciano, D. V. (2008). A decade's experience with temporary intravascular shunts at a civilian level I trauma center. *Journal of Trauma - Injury, Infection and Critical Care,* 65**,** 316-324.

Sunderland, S. (1951). A classification of peripheral nerve injuries producing loss of function. *Brain,* 74**,** 491-516.

Sutton, A. J. & Abrams, K. R. (2001). Bayesian methods in meta-analysis and evidence synthesis. *Statistical Methods in Medical Research,* 10**,** 277-303.

Swets, J. A. (1988). Measuring the accuracy of diagnostic systems. *Science,* 240**,** 1285-1293.

Talving, P., Benfield, R., Hadjizacharia, P., Inaba, K., Chan, L. S. & Demetriades, D. (2009). Coagulopathy in severe traumatic brain injury: A prospective study. *Journal of Trauma - Injury, Infection and Critical Care,* 66**,** 55-61.

Tan, T. W., Joglar, F. L., Hamburg, N. M., Eberhardt, R. T., Shaw, P. M., Rybin, D., Doros, G. & Farber, A. (2011). Limb outcome and mortality in lower and upper extremity arterial injury: a comparison using the National Trauma Data Bank. *Vascular and Endovascular Surgery,* 45**,** 592-597.

Tintle, S. M., Baechler, M. F., Nanos 3rd, G. P., Forsberg, J. A. & Potter, B. K. (2010a). Traumatic and trauma-related amputations: Part II: Upper extremity and future directions. *Journal of Bone & Joint Surgery, American volume,* 92**,** 2934-2945.

Tintle, S. M., Keeling, J. J., Shawen, S. B., Forsberg, J. A. & Potter, B. K. (2010b). Traumatic and trauma-related amputations: part I: general principles and lower-extremity amputations. *Journal of Bone & Joint Surgery, American volume,* 92**,** 2852-2868.

Tonelli, M. R. (1998). The philosophical limits of evidence-based medicine. *Academic Medicine,* 73**,** 1234-1240.

Topal, A. E., Eren, M. N. & Celik, Y. (2010). Lower extremity arterial injuries over a six-year period: outcomes, risk factors, and management. *Vascular Health and Risk Management,* 6**,** 1103-1110.

Tversky, A. & Kahneman, D. (1974). Judgment under uncertainty: Heuristics and biases. *Science,* 185**,** 1124-1131.

UN. (2012). World economic situation and prospects 2012. New York, N.Y.: United Nations. Department of Economic and Social Affairs.,
United Nations Conference on Trade and Development.,.

Van Gerven, M. A. J., Taal, B. G. & Lucas, P. J. F. (2008). Dynamic Bayesian networks as prognostic models for clinical patient management. *Journal of Biomedical Informatics,* 41**,** 515-529.

Vertrees, A., Fox, C. J., Quan, R. W., Cox, M. W., Adams, E. D. & Gillespie, D. L. (2009). The use of prosthetic grafts in complex military vascular trauma: a limb salvage strategy for patients with severely limited autologous conduit. *Journal of Trauma - Injury, Infection and Critical Care,* 66**,** 980-983.

Vittinghoff, E. & McCulloch, C. E. (2007). Relaxing the rule of ten events per variable in logistic and Cox regression. *American Journal of Epidemiology,* 165**,** 710-718.

Von Korff, M., Ormel, J., Keefe, F. J. & Dworkin, S. F. (1992). Grading the severity of chronic pain. *Pain,* 50**,** 133-149.

Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J. A., Abdalla, S., Aboyans, V., et al. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet,* 380**,** 2163-2196.

Wafaisade, A., Wutzler, S., Lefering, R., Tjardes, T., Banerjee, M., Paffrath, T., Bouillon, B. & Maegele, M. (2010). Drivers of acute coagulopathy after severe trauma: A multivariate analysis of 1987 patients. *Emergency Medicine Journal,* 27**,** 934-939.

Wagels, M., Rowe, D., Senewiratne, S. & Theile, D. R. (2013). History of lower limb reconstruction after trauma. *ANZ Journal of Surgery,* 83**,** 348-353.

Walsh, T. S., Stanworth, S. J., Prescott, R. J., Lee, R. J., Watson, D. M. & Wyncoll, D. (2010). Prevalence, management, and outcomes of critically ill patients with prothrombin time prolongation in United Kingdom intensive care units*. *Critical Care Medicine,* 38**,** 1939-1946.

Wang, H. E., Callaway, C. W., Peitzman, A. B. & Tisherman, S. A. (2005). Admission hypothermia and outcome after major trauma. *Critical Care Medicine,* 33**,** 1296-1301.

Warn, D., Thompson, S. & Spiegelhalter, D. (2002). Bayesian random effects meta‐analysis of trials with binary outcomes: methods for the absolute risk difference and relative risk scales. *Statistics in Medicine,* 21**,** 1601-1623.

Watson, G. A., Sperry, J. L., Rosengart, M. R., Minei, J. P., Harbrecht, B. G., Moore, E. E., Cuschieri, J., Maier, R. V., Billiar, T. R. & Peitzman, A. B. (2009). Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *Journal of Trauma - Injury, Infection and Critical Care,* 67**,** 221-230.

Watts, D. D., Trask, A., Soeken, K., Perdue, P., Dols, S. & Kaufmann, C. (1998). Hypothermic coagulopathy in trauma: Effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity. *Journal of Trauma - Injury, Infection and Critical Care,* 44**,** 846-854.

Way, L. W., Stewart, L., Gantert, W., Liu, K., Lee, C. M., Whang, K. & Hunter, J. G. (2003). Causes and prevention of laparoscopic bile duct injuries: analysis of 252 cases from a human factors and cognitive psychology perspective. *Annals of Surgery,* 237**,** 460.

Webb, L. X., Bosse, M. J., Castillo, R. C. & MacKenzie, E. J. (2007). Analysis of surgeon-controlled variables in the treatment of limb-threatening type-III open tibial diaphyseal fractures. *Journal of Bone & Joint Surgery, American volume,* 89**,** 923-928.

Wegener, S. T., Castillo, R. C., Haythornthwaite, J., Mackenzie, E. J., Bosse, M. J. & Group, L. S. (2011). Psychological distress mediates the effect of pain on function. *Pain,* 152**,** 1349-1357.

Weigel, A. P., Liniger, M. A. & Appenzeller, C. (2007). The discrete Brier and ranked probability skill scores. *Monthly Weather Review,* 135.

Whitaker, I. S., Rozen, W. M. & Shokrollahi, K. (2011). The management of open lower limb fractures: the journey from amputation to evidence-based reconstruction and harpsichords. *Annals of Plastic Surgery,* 66**,** 3-5.

White, J. M., Stannard, A., Burkhardt, G. E., Eastridge, B. J., Blackbourne, L. H. & Rasmussen, T. E. (2011a). The epidemiology of vascular injury in the wars in Iraq and Afghanistan. *Annals of Surgery,* 253**,** 1184-1189.

White, N., Martin, E., Reynolds, P., Barbee, R., Brophy, D. & Ward, K. (2010a). Defining the effects of tissue hypoperfusion on clot strength in a swine model of traumatic shock. *Shock,* 33**,** 28-29.

White, N. J., Leong, B. S., Brueckner, J., Martin, E. J., Brophy, D. F., Peberdy, M. A., Ornato, J. & Ward, K. R. (2011b). Coagulopathy during cardiac arrest and resuscitation in a swine model of electrically induced ventricular fibrillation. *Resuscitation,* 82**,** 925-931.

White, N. J., Martin, E. J., Brophy, D. F. & Ward, K. R. (2010b). Coagulopathy and traumatic shock: Characterizing hemostatic function during the critical period prior to fluid resuscitation. *Resuscitation,* 81**,** 111-116.

WHO. (2014). Injuries and violence: the facts 2014. Geneva: World Health Organisation.

Wieslander, J. B., Wendeberg, B., Linge, G., Buttazzoni, G. & Buttazzoni, A. M. (1996). Tissue expansion: a method to preserve bone length and joints following traumatic amputations of the leg--a follow-up of five legs amputated at different levels. *Plastic and Reconstructive Surgery,* 97**,** 1065-1071.

Wolberg, A. S., Meng, Z. H., Monroe, D. M., 3rd & Hoffman, M. (2004). A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. *Journal of Trauma - Injury, Infection and Critical Care,* 56**,** 1221-1228.

Woodward, E. B., Clouse, W. D., Eliason, J. L., Peck, M. A., Bowser, A. N., Cox, M. W., Jones, W. T. & Rasmussen, T. E. (2008). Penetrating femoropopliteal injury during modern warfare: experience of the Balad Vascular Registry. *Journal of Vascular Surgery,* 47**,** 1259-1264; discussion 1264-1255.

Wyatt, J. C. & Altman, D. G. (1995). Commentary: Prognostic models: clinically useful or quickly forgotten? *British Medical Journal,* 311**,** 1539-1541.

Xu, S. X., Wang, L., Zhou, G. J., Zhang, M. & Gan, J. X. (2013). Risk factors and clinical significance of trauma-induced coagulopathy in ICU patients with severe trauma. *European Journal of Emergency Medicine,* 20**,** 286-290.

Yahya, M. M., Mwipatayi, B. P., Abbas, M., Rao, S. & Sieunarine, K. (2005). Popliteal artery injury: Royal Perth experience and literature review. *ANZ Journal of Surgery,* 75**,** 882-886.

Yet, B. (2013). *Bayesian Networks for Evidence Based Clinical Decision Support.* Doctor of Philosophy PhD Thesis, Queen Mary, University of London.

Yet, B., Perkins, Z., Fenton, N., Tai, N. & Marsh, W. (2014a). Not just data: A method for improving prediction with knowledge. *Journal of Biomedical Informatics,* 48**,** 28-37.

Yet, B., Perkins, Z., Tai, N. & Marsh, W. (2014b). Explicit Evidence for Prognostic Bayesian Network Models. *EHealth-For Continuity of Care: Proceedings of MIE2014,* 205**,** 53 - 57.

Yet, B., Perkins, Z. B., Rasmussen, T. E., Tai, N. R. & Marsh, D. W. (2014c). Combining data and meta-analysis to build Bayesian networks for clinical decision support. *Journal of Biomedical Informatics,* 52**,** 373-385.

Younesi, E. & Hofmann-Apitius, M. (2013). From integrative disease modeling to predictive, preventive, personalized and participatory (P4) medicine. *The EPMA journal,* 4**,** 23.

Yule, S., Flin, R., Paterson-Brown, S. & Maran, N. (2006). Non-technical skills for surgeons in the operating room: a review of the literature. *Surgery,* 139**,** 140-149.

Zehtabchi, S., Soghoian, S., Liu, Y., Carmody, K., Shah, L., Whittaker, B. & Sinert, R. (2008). The association of coagulopathy and traumatic brain injury in patients with isolated head injury. *Resuscitation,* 76**,** 52-56.

Zhu, Y. L., Xu, Y. Q., Li, J., Wang, Y. & Luo, G. (2010). Medial approach for popliteal artery injuries. *Chinese Journal of Traumatology,* 13**,** 83-86.

Zsambok, C. E. & Klein, G. (2014). *Naturalistic decision making*, Psychology Press.

APPENDIX I

PROSPERO
International prospective register of systematic reviews

NHS
National Institute for Health Research

A systematic review of prognostic factors related to secondary amputation in patients with lower limb vascular trauma requiring surgical repair

Zane Perkins, Simon Glasgow, Nigel Tai

Citation
Zane Perkins, Simon Glasgow, Nigel Tai. A systematic review of prognostic factors related to secondary amputation in patients with lower limb vascular trauma requiring surgical repair. PROSPERO 2012:CRD42012002720 Available from **http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002720**

Review question(s)

The objective of this review is to develop a more reliable overall assesment of the injury and clinical factors predictive of secondary amputation in patients with traumatic lower limb vascular injuries.

Searches

Information sources:

a) Electronic Databases: MEDLINE, EMBASE, CINAHL

b) Manual search of relevant reference lists

Limits:

a) Date: 01/01/2000 - 01/06/2012

b) Human

c) Language: English

Types of study to be included

Include:

Cohort studies, observational studies, case series with greater than 5 patients; systematic reviews.

Exclude:

Case series with 5 or less patients; case reports; narrative/expert reviews, letters and editorials.

Condition or domain being studied

Trauma is the leading cause of death and disability in societies' young and most active members. Severe lower limb injuries, including limb amputations, are an important source of this disability. Secondary amputations are amputations performed after an initial attempt to salvage the limb.

Participants/ population

Inclusion:

a) Adult patients (>16 years), AND

b) Acute traumatic injury, AND

c) Lower limb major vascular injury (external iliac to tibial vessels), AND

d) Attempted surgical repair using standard vascular surgery techniques.

Exclusions:

a) Children

b) Not an acute traumatic injury: iatrogenic injuries, pathological changes following spinal injury, longstanding complications of traumatic vascular injuries, peripheral vascular disease.

c) Non-surgical management: Injuries treated conservatively or with interventional radiology techniques, injuries treated with experimental or non-standard surgical techniques.

Intervention(s), exposure(s)

Prognostic factors related to secondary amputation:

a) Injury related factors: Mechanism of injury (blunt/penetrating); anatomical segment of vessel injured; associated vein/bone/soft tissue injury; associated shock.

b) Treatment related factors: ischaemic time; surgical procedure; prophylactic faciotomy; temporary shunt.

c) Complications: Infection; graft failure.

Comparator(s)/ control
Comparator will be lower limb vascular injuries requiring surgical repair where the prognostic factor is not present.

Outcome(s)

Primary outcomes
Secondary amputation. Defined as an amputation performed after a surgical attempt at vascular repair (salvage) has occurred.

Outcome is occurrence of secondary amputation (binary), regardless of time.

Secondary outcomes
None

Data extraction, (selection and coding)
Two independent reviewers will screen all citations for possible relevance. All identified citations from either reviewer will be assessed for inclusion eligibility. Both reviewers will then independently apply inclusion/exclusion criteria; discrepancies will be resolved by discussion and consensus.

Risk of bias (quality) assessment
Quality assessment:

Key components of study design and reporting related to the study question (population, prognostic factors, outcome, study design) will be appraised. This will include an assessment of the description of the study population, prognostic factors and outcome; definitions used; length of follow-up, standard treatment, study design, level of care and year of study.

Performance bias will be assessed by subgroup analysis (Level of care; Military vs. Civilian).

Measurement bias will be assessed based on the outcome definition.

Strategy for data synthesis
a) Descriptive summary of the included studies' key characteristics.

b) Collate and summarise the observed effects (Qualitative). Where possible, an odds ratio (95% CI) will be calculated in individual studies as a measure of the strength of the relationship between the prognostic factor and outcome. If sufficient similar studies are available, a meta-analysis of studies with available/calculated odds ratios will be performed using a random-effect model.

c) If there is a sufficient pool of data on individual patients, a multiple regression analysis will be performed to control for confounding.

d) Statistical heterogeneity will be calculated using the chi-squared test and I-squared index.

Analysis of subgroups or subsets
Military vs. Civilian outcomes.

Level 1 trauma unit (or equivalent) vs. other hospitals outcomes

Contact details for further information
Zane Perkins

Trauma Clinical and Academic Unit

The Royal London Hospital

Whitechapel Road,

London,

E1 1BB

zaneperkins@gmail.com

Organisational affiliation of the review
Trauma Sciences. Queen Mary, University of London

http://www.smd.qmul.ac.uk/research/neuro/traumascience/index.html

Review team
Mr Zane Perkins, Trauma Sciences. Queen Mary, University of London

Dr Simon Glasgow, Trauma Sciences. Queen Mary, University of London
Mr Nigel Tai, Trauma Sciences, Queen Mary, University of London

Anticipated or actual start date
01 March 2012

Anticipated completion date
31 October 2012

Funding sources/sponsors
Trauma Sciences, Barts and the London School of Medicine and Dentistry, Queen Mary, University of London.

Academic Department of Military Surgery & Trauma (ADMST)

Conflicts of interest
None known

Language
English

Country
England

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Amputation; Blood Vessels; Humans; Lower Extremity; Prognosis; Vascular Surgical Procedures

Date of registration in PROSPERO
30 July 2012

Date of publication of this revision
31 July 2012

Stage of review at time of this submission	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No
Prospective meta-analysis	No	No

APPENDIX II

Data Extraction: Prognostic Factors for Secondary Amputation

Author:	**Year:**	**Journal:**
Title:		

Study design:	Single centre / Multiple centres
Setting: Civilian / Military / Mixed	**Recruitment period**:
Country of origin:	**UN Classification:** Developed / Developing

Sample Size:	**Specialist Centre:** Y / N	**Duration of Follow-up:**
Population:		

Surgical intervention described?	Yes / No / Unclear
Non-standard or non-surgical intervention?	Yes / No / Unclear
Secondary amputation appropriately defined / described?	Yes / No / Unclear

Number of limbs with surgical repair of LEVT	
Number of secondary amputations	

Notes:

Prognostic Factor (PF):	Definition:	Number of patients with PF		Number of patients w/out PF	
		Salvage	2nd Amp	Salvage	2nd Amp