Title. A National Study of Multiple Organ Dysfunction after Trauma: Contemporary Subtypes of Severity and Recovery

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ABSTRACT

***Background*.** The nature of Multiple Organ Dysfunction Syndrome (MODS) after traumatic injury is evolving as resuscitation practices advance and more patients survive their injuries to reach critical care. We aimed to characterise contemporary MODS subtypes in trauma critical care at a population level.

***Methods*.** Adult patients admitted to major trauma centre critical care units were enrolled in this four-week point-prevalence study**.** MODS was defined as daily total Sequential Organ Failure Assessment (SOFA) score >5. Hierarchical clustering of SOFA scores over time was used to identify MODS subtypes.

***Results*.** 440 patients were enrolled, of which MODS developed in 245 (56%). MODS carried a high mortality (22% vs. 1%, p<0.001) and 24% of deaths occurred early, within the first 48 hours after injury. Three patterns of MODS were identified, all present on admission. Cluster 1 MODS resolved early with a median time to recovery of four days and a mortality of 14%. Cluster 2 had a delayed recovery (median 13 days) and mortality of 35%. Cluster 3 had a prolonged recovery (median 25 days) and high associated mortality of 46%. Multivariable analysis revealed distinct clinical associations for each form of MODS, with 24-hour crystalloid administration strongly associated with Cluster 1 (p<0.001); traumatic brain injury with Cluster 2 (p<0.01); and admission shock severity with Cluster 3 (p<0.01).

***Conclusions*.** Contemporary MODS has at least three distinct types based on patterns of severity and recovery. Further characterisation of MODS subtypes and their underlying pathophysiology may lead to future opportunities for early stratification and targeted interventions.

INTRODUCTION

Multiple Organ Dysfunction Syndrome (MODS) is common in critically injured trauma patients who survive the initial insult, and is associated with poor outcomes(1). MODS is responsible for a large proportion of the healthcare resources associated with acute trauma care(2). As early-phase management strategies such as damage control resuscitation have been introduced and more trauma patients are surviving to reach critical care the nature of MODS appears to be changing (3). Reports of differences in patterns of evolution, severity and outcome are challenging the previously accepted clinical concepts of 'early and late onset' or bimodal peaks of MODS (4-9). Determining the incidence, patterns, and outcomes of MODS in the modern era may help to identify therapeutic opportunities and inform study design for future research.

With more early survivors of severe injury, MODS remains a determinant of poor outcomes and a continued challenge for trauma systems (2, 7). The pathophysiology of MODS is a subject of debate in the literature. Some of the uncertainty may be due to the existence of discrete forms of MODS with unique pathophysiologies. Recent studies have described protracted forms of MODS associated with aging, immunosuppression, infection and catabolism (4, 10, 11). The national incidence of these contemporary MODS subtypes, their resource utilization and associated outcomes are not known. Characterizing these different MODS subtypes is important if progress is to be made in understanding their underlying pathophysiologies, in developing new diagnostic and therapeutic approaches, and for the design of clinical studies in which to test them.

The overall aim of this study was to characterise contemporary MODS subtypes in trauma critical care at a population level. Our primary aim was to establish the overall incidence of

MODS, describe patterns of severity and recovery, and their associated outcomes. We specifically wished to examine different patterns of MODS onset and recovery. Our subsequent aim was to describe admission characteristics associated with any identified MODS subtypes. We conducted a point-prevalence study of patients admitted to critical care in major trauma centres in the United Kingdom.

METHODS

Study sites and participants

England, Wales and Scotland have an organised system of regional trauma networks, each with a Major Trauma Centre (MTC) (Level One equivalent) designated to manage the most severely injured patients in a geographical region. In the UK, MTCs should adhere to trauma resuscitation guidelines from the National Institute of Clinical Excellence(12). All MTCs were invited to participate and adult trauma patients (≥16 years) requiring admission to a critical care unit from 00:01h 1st June to 23.59h 30th June 2016 were eligible for inclusion. Study approval was provided by the NHS Research Ethics Committee (REC), Health Research Authority and Scotland REC A, ref: 15/SS/0170. Patients were enrolled into the study after admission to critical care, and informed consent was obtained from the patient or a consultee.

Study procedures

Procedures and training were provided via the Organ Dysfunction in Trauma (ORDIT) study webpages(13). Data on demographic characteristics, injury severity, admission physiology

and 24 hour resuscitation were recorded. Patients were reviewed daily in critical care until discharge or death.

Definitions

The presence and evolution of Multiple Organ Dysfunction Syndrome (MODS) was determined with Sequential Organ Failure Assessment (SOFA) scoring (14, 15). SOFA was chosen for wide utilisation in international critical care. It has been validated for use in trauma patients including studies applying it from day of admission (16) and has a good balance of sensitivity and specificity in predicting unfavourable outcome after severe injury (14). SOFA scores were measured daily from admission as described in earlier critical care studies (16-18). MODS was defined as the occurrence of a total SOFA score greater than five, affecting two or more organs (1, 4, 19). Recovery was when the SOFA score fell and remained below six. Traumatic Brain Injury (TBI) was classified as a head abbreviated injury score (AIS) of greater than or equal to three. Secondary outcomes were in-hospital mortality, ventilator days, critical care and hospital length of stay (LOS).

Data analysis

Data analysis was conducted using IBM SPSS Statistics (Version 21). Categorical variables were analysed using Chi-squared or Fishers Exact tests. Continuous data was non-parametric according to the Shapiro-Wilk tests and analysed with Mann-Whitney U and Kruskall Wallis tests. Multiple comparisons of individual pairs were analysed with Bonferroni corrections. Unsupervised hierarchical clustering was performed to define MODS cohorts using Morpheus online software (Broad Institute, MA). Previous clinical studies have utilised

hierarchical clustering analysis to classify patients within a population into discrete clusters or phenotypes on the basis of clinical data (18, 20, 21). Raw total SOFA score data for each patient on each day 1-28 (or day of critical care discharge/death if earlier) were entered into the data matrix. A SOFA score of 0 was assigned on discharge from ICU (unless readmitted). In patients who died during the 28-day period, no score was allocated after the date of death. These data were treated as missing in the clustering analysis and were excluded from all computations involving the rows within which they occurred. Heatmaps were generated using Euclidean distance between observations and complete linkage between clusters. Complete linkage has been reported to produce more meaningful separation between clusters than average linkage (22, 23) and standard Grubbs test was used to identify outliers (24). We chose the number of clusters by subjectively selecting a single threshold height that maintained reasonable sub-cluster sample size. The sensitivity and specificity of the clusters ability to detect MODS on each day was used to determine serial Youden indices and reported as sensitivity + specificity −1.

Multivariable logistic regression models were used to describe the association between admission or treatment variables and MODS. Variables with $p<0.1$ on univariate testing were entered into the regression analysis. Results are presented as Odds Ratios (OR) with 95% Confidence Intervals (CI). The calibration and goodness of fit of the logistic regression models were evaluated using the chi squared Hosmer-Lemeshow (HL) test, and model discrimination was assessed using area under the receiver–operator characteristic (AUROC) curves. Correlations between crystalloid use and MODS are described using Spearman's rank correlation coefficients.

RESULTS

All 29 adult major trauma centres in England, Wales and Scotland participated in the study. In total 446 patients were admitted to critical care during the one-month period, of which six died within the first 24 hours from injury. Of the remaining 440 patients, 56% (245) developed MODS (Table 1). The onset of MODS was on the day of admission in the majority of patients (94%). The remainder developed MODS on day two (5%) or day three (1%). Only two patients experienced a second episode of MODS, one at day seven and one at day 11. Average admission SOFA was 8.5 (95% CI 8.2-8.8), and severity peaked on day two at 8.8 (95% CI 8.5-9.1). Respiratory and cardiovascular dysfunction were the greatest contributors to MODS (97% and 91% of patients), followed by central nervous systems (CNS) (88%). Coagulation dysfunction affected 58%, whilst liver and renal systems had the lowest incidence of dysfunction (37% and 27% respectively). Organ dysfunction patterns were similar in patients with and without TBI (Table E1 and Figures E1-E2 in the online data supplement). 22% of patients with MODS died, compared to less than 1% of the no-MODS group (Table 1). In the 310 (70%) patients without TBI, MODS mortality was 15% compared to <1% without MODS (Table E1). The overall median time to death with MODS was six days (IQR 2-10) and 24% of all MODS deaths occurred within the first 48 hours. For survivors, average time in MODS was 10 days (IQR 5-17). In total, the 245 patients with MODS utilized 2656 critical care bed days and 5872 hospital days.

Hierarchical clustering analysis of daily SOFA scores identified three high-level clusters of different patient recovery patterns (Figure 1). Cluster 1 was the largest with 362 patients, of which 167 developed MODS (68% of all MODS patients). All 54 patients in Cluster 2

developed MODS (22%), as did the 24 patients in Cluster 3 (10%). Admission SOFA scores for patients in MODS were higher in Clusters 2 and 3 (Day 1 mean SOFA score: Cluster 1 7.7 vs. Cluster 2 8.9 p=0.002, vs. Cluster 3 10.9, p<0.001). SOFA scores of MODS patients in Cluster 1 immediately began improving and in survivors had fallen below MODS thresholds by day five. SOFA scores initially worsened for patients in Clusters 2 and 3 before beginning to resolve from day three, not falling below admission levels until day five (Figure 2A). Patterns of recovery did not appear to be affected by the presence of TBI (Figure 2B). MODS in Cluster 2 patients took longer to resolve (median 13 days, IQR 12-16), while Cluster 3 had a very protracted duration of organ dysfunction (median 25 days, IQR 19-28)(Figure 2C).

MODS had resolved in 92% of patients (120/131) in Cluster 1 by day seven, and no patients in this cluster remained in MODS after 11 days. MODS patients in Cluster 1 were best discriminated from those in Clusters 2 and 3 by their MODS status on day eight. 88% of patients still in MODS at day eight were in Clusters 2 or 3 (Sensitivity 99%, Specificity 93% for Clusters 2/3, Youden 0.91). Day 18 was the best discriminator between patients in Clusters 2 and 3, and 79% of patients still in MODS at day 18 were in Cluster 3 (Sensitivity 85%, Specificity 94% for being in Cluster 3, Youden 0.78).

The different patient clusters also had differing outcome profiles. Within Cluster 1 MODS patients had a 14**%** mortality, rising to 35% in Cluster 2 (p<0.001) and 46% in Cluster 3 (p<0.001, Table 1). Critical care stay for patients in Cluster 3 was double that of those in Cluster 2 (Cluster 2 vs 3: 20 vs. 36 days, p<0.001) and hospital stay was almost 40% longer (Cluster 2 vs 3: 39 vs. 53 days, p=0.030) (Table 1).

We analysed admission characteristics associated with the development of MODS in each cluster. Cluster 1 MODS was the only cluster where the development of MODS was not associated with injury severity (Table 2), despite high injury severity scores (median ISS 25, Table 1). The Cluster 1 MODS group was most strongly associated with the volume of crystalloid administered within the first 24 hours (Odds Ratio 2.8, Table 2, Figure 2D). Cluster 2 contained the greatest proportion of patients with TBI (59%, Figure 2E) and brain injury was strongly associated with this cluster (Odds Ratio 15.8, Table 2). Patients in Cluster 3 were the only MODS subtype who were shocked on arrival (median BD: 7.6mmol/l vs. 0mmol/l in all other MODS clusters, p=0.004, Figure 2F). Both admission base deficit and 24-hour crystalloids were independently associated with the development of prolonged MODS in Cluster 3 (Odds Ratio 1.11, p=0.003; Odds Ratio 1.24, p=0.019), Table 2).

We explored the potential effect of crystalloid by examining variation in practice across the study sites. The median crystalloid administration in MODS patients varied across sites from 1 to 5.2 litres whilst the incidence of MODS ranged from 8% to 100% (Figure 3A, Table E2). There was a strong correlation between individual site crystalloid use and the development of MODS in Cluster 1 (Spearman r0.65, p<0.001). A modest correlation was seen in Cluster 3 (Spearman r0.56, p=0.001), but not for Cluster 2 (Spearman r0.15, p=0.424) (Figure 3B). Overall, MODS resolved in a shorter time for patients who received less than 1.5L of crystalloid in the first 24 hours compared to those receiving greater volumes (Figure 3C). By day eight from injury almost twice the proportion of patients who had received more than 1.5L of crystalloid were still in MODS compared to those who had received 0-1.5L (≤1.5L vs. >1.5L: 19% vs. 36%, p=0.010). Critical care stay was longer for patients with MODS

receiving greater than 1.5L of crystalloid in the first 24 hours (≤1.5L vs. >1.5L: 5 vs. 7 days, p<0.001, Table E3).

DISCUSSION

This was a national point-prevalence study of MODS after traumatic injury in the era of contemporary damage control resuscitation, neurocritical care and regional trauma systems. MODS was common in this critical care population and had a high associated mortality and resource utilization. 7,604 trauma patients were admitted to critical care units in England and Wales in 2016 (source: Trauma Audit & Research Network, https://www.tarn.ac.uk/). Nationally we would therefore predict over 3300 trauma patients in critical care with MODS annually, requiring 33,000 critical care bed days, of which 750 will die. Survivors will require 63,750 hospital days and may suffer long-term impairment to physical and psychological outcomes (25).

Overall outcomes appear to have improved for patients with MODS in comparison to previous studies. Our MODS mortality of 22% compares with 33 - 36% in a study from the Glue Grant consortium in the USA which examined temporal trends in patients with MODS between 2003 and 2010(2). In our study there was a preponderance of cardiovascular dysfunction in the initial days after injury. Given that 34% of deaths occurred in this timeframe, it may be that cardiovascular dysfunction is the major component of MODS in the damage control resuscitation era.

MODS in our trauma patients appeared to be present on the first day of admission and had at least three distinct recovery patterns, an early resolving form and two types of persistent MODS. 31 patients (7% of total) with Cluster 1 MODS had resolved within the first 48 hours, and this group would not have been included in other studies which define MODS as occurring after day 2. In contrast, nearly a third of MODS patients in our study had a prolonged form of MODS (Cluster 2 or 3) taking a median of 15 days to resolve. Historically MODS has had a bimodal distribution with a second peak in incidence occurring between seven and 14 days after injury(26). This second peak has been declining (9) and appears to have all but disappeared in contemporary MODS with only three patients in our study developing MODS after day three. Contemporary MODS is characterized by respiratory, cardiovascular and haemostatic dysfunction. Respiratory and cardiovascular dysfunction were nearly universal in our MODS patients, whereas older studies have described involvement of these organ systems at around 50%(2). Patients with different recovery trajectories were indistinguishable on admission solely by examination of total or component SOFA scores, but there were differences in injury patterns, shock severity and early management associated with the subsequent development of these MODS subtypes.

Crystalloid use in the first 24 hours from injury was the only clinical variable associated with the Cluster 1 early resolving MODS subtype. Crystalloids are known to have proinflammatory effects on coagulation and the endothelium (27-29), and volume of administration is associated with increased organ injury such as ARDS and abdominal compartment syndrome. Previous trauma studies report the link between organ dysfunction and large volumes of crystalloid in the first 12 or 24 hours following injury (30,

31). Current national trauma haemorrhage guidance reflects this, recommending that crystalloids are avoided during damage control resuscitation(32). It is likely therefore that the majority of crystalloid administration occurs on the critical care unit. We only examined fluid use in the first 24 hours, but this effect may persist for some days, as time to resolution was almost double that of Cluster 1 patients without MODS. Further research is needed to explore causality in this relationship and identify optimal strategies for on-going volume replacement in these patients.

TBI characterised the group of patients whose MODS tended to persist, with a delayed recovery between days eight and 18. Brain injury is thought to potentially confound the assessment of MODS and its resolution (14, 33). In this study there is little to differentiate patients with and without MODS in terms of their severity or pattern of TBI. However, patients with TBI and MODS appear to have a specific, separate clinical trajectory, not limited to the CNS component of the SOFA score alone. Further investigation is required to determine whether this is due to extracranial effects of TBI or current management paradigms. For example endogenous or exogenous catecholamines have both been postulated as responsible for some of the observed effects (34-36). The presence of MODS is known to worsen outcomes for those with severe TBI (37, 38), therefore research focusing on this specific group of patients may unlock underlying mechanisms and lead to real improvements for brain injured patients.

Patients in Cluster 3 with the prolonged form of MODS were the smallest cohort but had the worst outcomes and consumed a disproportionate amount of critical care resources. Previous studies of an indolent, immunosuppressive dysfunction have focused on elderly

patients (39, 40), but we found no difference in age between MODS clusters. Admission shock was only associated with the subsequent development of prolonged MODS found in Cluster 3. There was a weaker association with crystalloid administration in this group than in Cluster 1, and there was no association with the volume of blood product administration. These suggest that the persistent MODS in patients in Cluster 3 may be due to an early response to the shocked state, and not a later consequence of resuscitation. Prolonged MODS may represent the contemporary form of classical multiple organ failure, driven by dysregulation of the inflammatory response to injury (41). Developing biomarkers and stratification tools to identify these patients early in their clinical course may allow the development of new management strategies and therapeutic opportunities for MODS after injury.

There are a number of limitations to this study. While wide geographically, it was limited in its accrual period and the number of data-points captured for each patient. In particular, we were not able to capture the number and nature of infectious episodes or other complications which may have contributed to prolonged MODS. We were also not able to assign cause of death which would provide insight into if and how MODS contributed to the deaths of each patient. In the hierarchical clustering analysis, the selection of the number of clusters to analyse was based on a determination of adequate cluster size for intergroup analyses. Further subtypes may be identified from deeper analysis in larger cohorts of patients. Whilst the majority of deaths in the early resolving MODS group occurred within 48 hours, the patterns of deaths for the differing clusters require further evaluation. SOFA scoring differs from other MODS scores (such as the Denver(42) or Goris scores(43)) as it

contain CNS and coagulation components, which may lead to differences in reported incidence of MODS (33) and may partly account for differences in proportion of MODS in this study. However the use of SOFA in severely injured and TBI populations has a good discriminative ability and balance of sensitivity and specificity in predicting unfavourable outcome for trauma patients (14, 44). In our multivariable analyses examining associations of clinical variables with the development of MODS, there is potential overlap between SOFA components as both admission (input) and later SOFA (output) variables, such as the GCS. While GCS was associated with the overall development of MODS, this association was lost when analysing individual clusters and in Cluster 2 only was the anatomic presence of a head injury associated with MODS development. We therefore believe the analysis provides a robust signal for the associations across each analysis. As an observational study however, we can only identify associations of clinical variables with MODS but are unable to determine causation. In Cluster 3 there are only 24 outcomes which may lead to model over-fit. Larger cohort studies are required to explore these smaller cohorts, and potential further sub-cluster divisions. Finally, the multicentre nature of this study may mean differing treatment policies despite national guidance, therefore we our study represents clinically focused descriptors of MODS subtypes rather than ones driven by biology alone.

MODS is still common in the era of damage control resuscitation and has an associated mortality and high resource utilization. Contemporary MODS is now almost always present from admission, commonly involves cardiovascular dysfunction, and has subtypes with different patterns of recovery. Patients who will develop persistent MODS are difficult to identify on admission from their clinical characteristics. The development of tools for the early identification of these subtypes will require further research on their individual initiating mechanisms.

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TABLE 1. ADMISSION CHARACTERISTICS, INJURIES AND OUTCOMES

	ALL MODS	Cluster 1 No MODS	Cluster 1 MODS	Cluster 2 MODS	Cluster 3 MODS
n	**245**	**195**	**167**	**54**	**24**
Admission variables:					
Age	47 (29-65)	48 (29-63)	47 (29-68)	47 (28-60)	42 (28-57)
Male (%)	185 (76)	140 (72)	122 (73)	43 (80)	20 (83)
Blunt (%)	222 (91)	166 (85)	151 (90)	51 (94)	20 (83)
First GCS	13 (6-15)*	14 (9-15)	14 (6-15)	12 (4-15)	14 (9-15)
First SBP	125 (104-145)	127 (107-141)	125 (103-145)	125 (110-143)	128 (110-144)
First SBP <90mmHg (%)	23 (9)	11 (6)	19 (11)	2 (4)	2 (8)
First BD (mEq/L)	0.1 (0.4-6.7)*	0 (-1.2-1.1)	0 (-1.1-5.1)	0 (-0.2-5.0)	7.5 (0.3-11.1)
CSL L/24H	2.9 (2.0-4.5)*	1.2 (1.0-2.0)	3.0 (2.0-4.5)	2.3 (1.7-3.8)	3.7 (2.2-5.0)
RBC units/24H	4 (2-7)*	3 (2-4)	4 (2-6)	4 (2-7)	4 (2-11)
FFP units/24H	4 (2-8)*	3 (2-4)	4 (2-8)	4 (2-6)	4 (2-8)
FFP:RBC ratio	0.5 (0-1.0)	0.1 (0-0.6)	0.6 (0-1.0)	0.5 (0-1.0)	0.5 (0-0.8)
TBI (%)	99 (40)*	30 (15)	56 (34)	34 (63)	9 (38)
ISS	25 (18-36)*	17 (9-26)	25 (16-33)	29 (25-43)	31 (19-45)
APACHE II score	14 (10-20)	9 (6-13)	14 (10-19)	15 (10-22)	18 (11-24)
Outcomes:					
Mortality (%)	54 (22)	1 (<1)	24 (14)	19 (35)	11 (46)
Ventilator days	4 (2-11)	1 (1-2)	3 (1-5)	11 (10-15)	16 (12-24)
CCLOS	11 (5-19)	3 (2-5)	7 (4-14)	20 (16-27)	36 (32-47)
THLOS	26 (13-40)	9 (5-20)	22 (12-33)	39 (25-62)	53 (39-104)

Median (IQR) or n(%). Abbreviations = GCS: Glasgow Coma Scale; SBP: Systolic Blood Pressure; BD: Base Deficit; CSL: Crystalloid; RBC: Red Blood Cells; FFP: Fresh Frozen Plasma; TBI: Traumatic Brain Injury; ISS: Injury Severity Score; APACHE II: Acute Physiology and Chronic Health Evaluation II; CCLOS: Critical Care Length of stay; THLOS: Total Hospital Length of stay. Only 21 patients (5%) received colloids. Median (IQR) for All, No MODs and Clusters 1-3 were 0 (0-0). *signifies variables p<0.100 entered into multivariable analysis

TABLE 2. MULTIVARIABLE ANALYSIS OF FACTORS ASSOCIATED WITH THE DEVELOPMENT OF MODS

	All MODS		CLUSTER 1 MODS		CLUSTER 2 MODS		CLUSTER 3 MODS	
n	**245**		**167**		**54**		**24**	
Predictor	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
First GCS	1.06 (0.92-1.2)	0.374	1.02 (0.91-1.09)	0.960	0.93 (0.85-1.01)	0.091	-	-
First BD	1.04 (0.94-1.1)	0.408	1.02 (0.96-1.09)	0.424	0.99 (0.92-1.07)	0.851	1.1 (1.01-1.2)	0.003
CSL L/24H	3.0 (1.7-5.4)	0.000	1.3 (1.07-1.6)	0.009	0.99 (0.81-1.2)	0.928	1.2 (1.03-1.5)	0.019
RBC u/24h	1.2 (0.98-1.5)	0.069	1.02 (0.91-1.1)	0.705	-	-	-	-
FFP u/24h	1.1 (0.73-1.8)	0.516	1.1 (0.86-1.4)	0.370	-	-	-	-
TBI	4.2 (0.39-46.8)	0.232	2.0 (0.66-6.1)	0.474	3.5 (1.5-7.8)	0.002	0.98 (0.35-2.06)	0.973
ISS	1.06 (1.01-1.1)	0.007	1.01 (0.93-1.03)	0.513	1.03 (1.0-1.06)	0.015	1.03 (1.004-1.06)	0.036

Data presented as Odds Ratio (95% Confidence Intervals) and p values. Variables <0.1 in univariate analysis of All MODS group vs. NoMODS, or comparisons between Clusters 1-3 were entered into multivariable models. Abbreviations = GCS: Glasgow Coma Scale; BD: Base Deficit; CSL: Crystalloid; RBC: Red Blood Cells; FFP: Fresh Frozen Plasma; u: units; TBI: Trauma Brain Injury; ISS: Injury Severity Score. All patients model: AUROC 0.91 (95% CIs 0.85-0.97), Hosmer-Lemeshow test 8.9, p= 0.34; Cluster 1 model: AUROC 0.79 (0.61-0.88), Hosmer-Lemeshow test 5.8 p= 0.66; Cluster 2 model: AUROC 0.73 (0.63-0.82), Hosmer-Lemeshow test 4.4 p= 0.81; Cluster 3 model: AUROC 0.80 (0.72-0.88), Hosmer-Lemeshow test 7.0 p= 0.53.

Figure 1

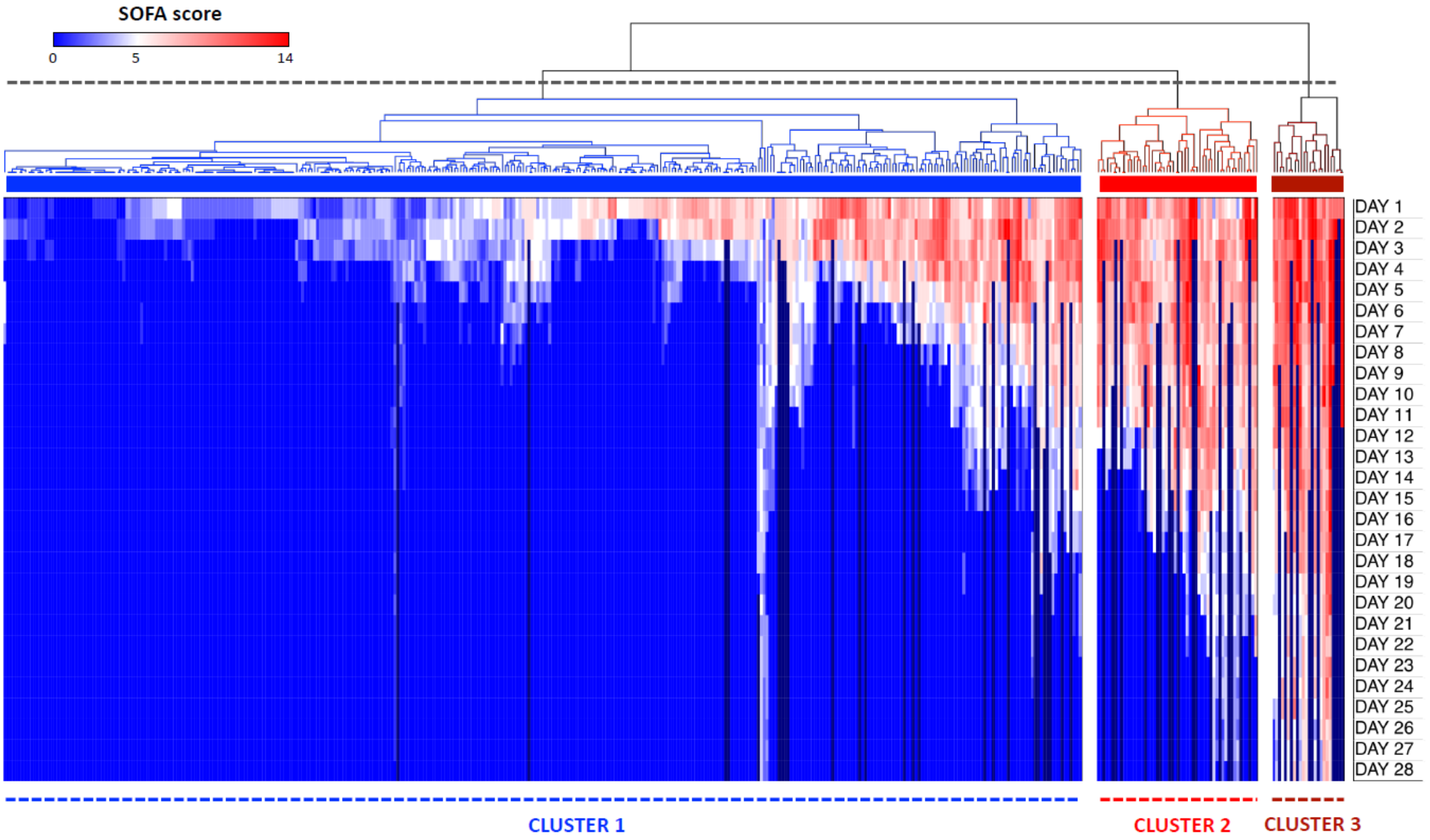

SOFA score
0
5
14
DAY 1
DAY 2
DAY 3
DAY 4
DAY 5
DAY 6
DAY 7
DAY 8
DAY 9
DAY 10
DAY 11
DAY 12
DAY 13
DAY 14
DAY 15
DAY 16
DAY 17
DAY 18
DAY 19
DAY 20
DAY 21
DAY 22
DAY 23
DAY 24
DAY 25
DAY 26
DAY 27
DAY 28
CLUSTER 1
CLUSTER 2
CLUSTER 3

Figure 2

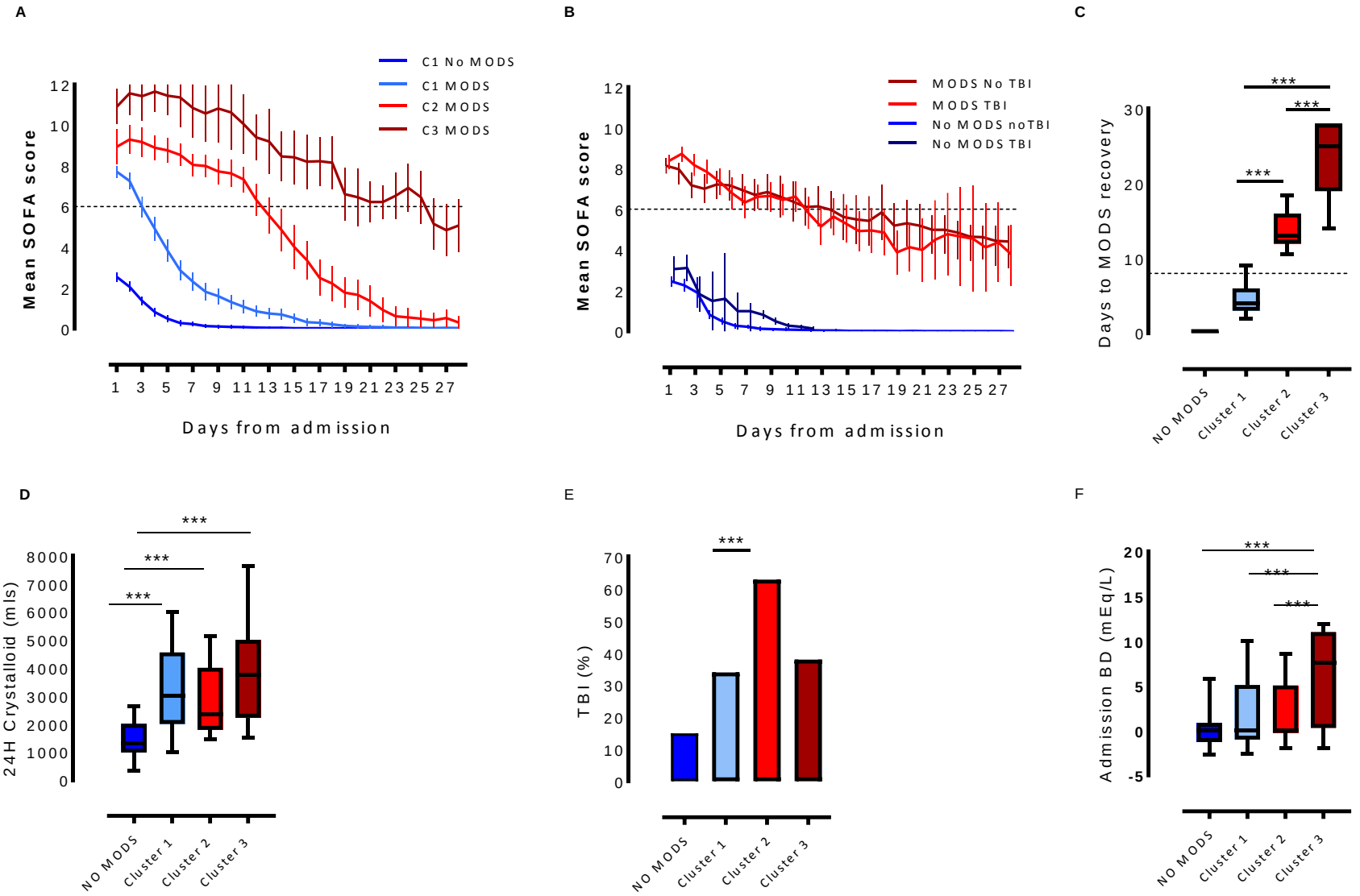

A
C1 No MODS
C1 MODS
C2 MODS
C3 MODS
Mean SOFA score
Days from admission
B
MODS No TBI
MODS TBI
No MODS noTBI
No MODS TBI
Mean SOFA score
Days from admission
C
Days to MODS recovery
NO MODS
Cluster 1
Cluster 2
Cluster 3
D
24H Crystalloid (mls)
E
TBI (%)
F
Admission BD (mEq/L)

Figure 3

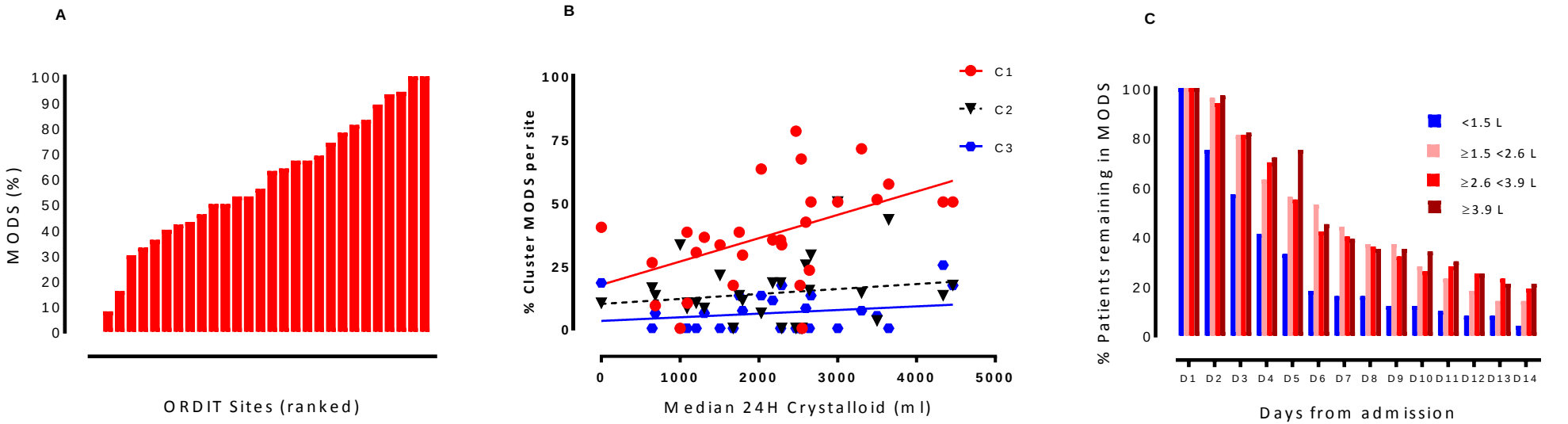

A
MODS (%)
100
90
80
70
60
50
40
30
20
10
0
ORDIT Sites (ranked)
B
% Cluster MODS per site
100
75
50
25
0
0
1000
2000
3000
4000
5000
Median 24H Crystalloid (ml)
C1
C2
C3
C
% Patients remaining in MODS
100
80
60
40
20
0
D1 D2 D3 D4 D5 D6 D7 D8 D9 D10 D11 D12 D13 D14
Days from admission
<1.5 L
≥1.5 <2.6 L
≥2.6 <3.9 L
≥3.9 L

Figure legends

Figure 1. Unsupervised hierarchical clustering of sequential organ failure assessment (SOFA) scores from admission to day 28. Shades of red within the heatmap indicate patients with MODS, defined as a SOFA score of ≥6. Patients discharged from critical care were assigned a score of 0 (blue). Patients who died within 28 days had missing scores after the date of death (black). Dashed line indicates the level of dendrogram transection used for analysis

Figure 2. A. Line graph shows mean (95% CI) SOFA scores by day of hospital admission for patients in Cluster 1 No MODS, Cluster 1 MODS, Cluster 2 MODS and Cluster 3 MODS. B. Line graph shows mean (95% CI) SOFA scores by day of hospital admission for patients with MODS without Traumatic Brain Injury (TBI), MODS with TBI, No MODS without TBI, No MODS with TBI. C. Box and whisker plots show time to resolution of MODS in survivors, defined as days from admission to first reaching a SOFA score <6. D. Box and whisker plots show 24 hour crystalloid per cluster. E. Bar graph shows proportion of patients with TBI (Head AIS≥3) per cluster. F. Box and whisker plots show admission base deficit per cluster. Data in figures C, D and F were analysed using Kruskall Wallis with multiple comparisons of selected cluster groups using Bonferroni correction. Cluster groups in figure E were compared using chi squared analysis. ***p<0.010

Figure 3. A. Bar graph shows % of patients who developed MODS per ORDIT site, ranked 0-100%. B. Scatter plot shows % of patients per site with MODS in Clusters 1, 2 and 3, plotted against median crystalloid (CSL) use per site. Correlation between All MODS and site CSL use: Spearman rho 0.66, p<0.001; Cluster 1 MODS: Spearman rho 0.65, p<0.001; Cluster 2 MODS: Spearman rho 0.15, p=0.42; Cluster 3 MODS:

Spearman rho 0.56, $p<0.001$. C. Bar graph shows % of patients remaining in MODS per day from injury within quartiles of initial 24 hour crystalloid administration.

TABLE E1. ADMISSION CHARACTERISTICS AND OUTCOMES FOR PATIENTS WITH AND WITHOUT TBI

	No TBI No MODS	**No TBI MODS**	**TBI No MODS**	**TBI MODS**
	164	***146***	***31***	***99***
Age	48 (27-62)	47 (30-59)	38 (24-63)	46 (28-65)
Male (%)	114 (70)	111 (76)	25 (81)	74 (75)
Blunt (%)	128 (78)	130 (89)	30 (97)	84 (85)
First GCS	15 (9-15)	14 (7-15)*	13 (3-15)	14 (6-15)
First SBP	121 (115-129)	119 (112-120)	132 (110-152)	127 (106-150)
Admission BD (mEq/L)	0 (-1.3-0.8)	0 (-0.8-6.4)**	0 (-1.3-4.2)	0.3 (-0.3-5.7)
CSL L/24H (L)	0.5 (0.2-1.3)	2.6 (1.5-3.8)**	0.6 (0.3-1)	2.8 (2.3-3.2)**
RBC units/24H	3 (2-5)	4 (2-8)*	1 (0-3)	3 (2-5)**
ISS	16 (9-26)	25 (13-30)**	24 (15-31)	29 (24-36)**
APACHE II score	9 (6-12)	14 (10-16)**	13 (7-16)	16 (10-23)*
Outcomes:				
Mortality (%)	1 (<1)	22 (15)**	0	32 (32)**
Ventilator days	1 (0-1)	3 (0-9)**	0 (0-2)	5 (2-11)**
CCLOS	3 (2-4)	9 (4-18)**	3 (2-5)	13 (6-21)**
THLOS	9 (5-20)	22 (12-39)**	11 (4-23)	29 (20-44)**

Median (IQR) unless otherwise specified. *p<0.050; **p<0.010 when comparing No MODS and MODS groups without and with TBI. Abbreviations = GCS: Glasgow Coma Scale; SBP: Systolic Blood Pressure; BD: Base Deficit; CSL: Crystalloid; RBC: Red Blood Cells; TBI: Traumatic Brain Injury; ISS: Injury Severity Score; APACHE II: Acute Physiology and Chronic Health Evaluation II; CCLOS: Critical Care Length of stay; THLOS: Total Hospital Length of stay.

TABLE E2. CHARACTERISTICS OF PATIENTS WITH MODS PER SITE

Site	N enrol	% MODS	% TBI	Age	First GCS	First SBP	ISS	APACHE II	N (%) mortality
1	34	56%	32%	54 (21-67)	7 (4-13)	124 (92-126)	29 (16-43)	11 (9-14)	2 (11)
3	9	78%	14%	49 (47-62)	13 (9-15)	115 (112-153)	29 (16-34)	19 (16-22)	0
4	30	40%	17%	63 (56-72)	13 (4-15)	127 (112-136)	36 (27-45)	13 (8-24)	6 (50)
5	6	50%	0%	61 (51-86)	8 (3-15)	129 (102-163)	14 (1-20)	14 (6-26)	1 (33)
6	7	100%	57%	41 (26-50)	9 (5-14)	114 (95-144)	18 (8-38)	26 (22-28)	0
7	11	64%	45%	55 (24-66)	9 (4-15)	130 (113-152)	38 (25-57)	17 (4-19)	1 (9)
8	10	50%	0%	46 (31-66)	13 (8-15)	100 (53-134)	29 (12-35)	11 (9-19)	0
9	19	42%	25%	39 (24-52)	12 (3-15)	106 (72-146)	39 (25-55)	15 (8-16)	1 (13)
10	10	30%	0%	52 (51-87)	15 (4-15)	122 (98-160)	16 (9-30)	11 (9-13)	2 (67)
11	14	93%	46%	30 (23-66)	7 (3-14)	123 (107-135)	43 (32-46)	10 (7-14)	2 (15)
12	19	16%	0%	56 (26-74)	8 (7-14)	121 (108-153)	27 (16-38)	10 (6-28)	2 (33)
13	16	81%	0%	56 (43-72)	11 (7-15)	126 (103-133)	25 (18-39)	19 (16-22)	2 (15)
14	3	67%	0%	55 (36-73)	14 (14-15)	134 (130-137)	10 (9-10)	12 (6-18)	0
15	39	74%	59%	37 (26-63)	9 (6-15)	122 (104-152)	29 (25-34)	11 (9-15)	4 (10)
16	6	83%	0%	34 (28-48)	14 (10-15)	110 (95-139)	9 (9-25)	8 (5-19)	0
17	12	8%	0%	18	15	88	29	12	0
18	14	43%	33%	46 (41-77)	8 (3-15)	132 (128-142)	18 (8-28)	14 (10-26)	2 (33)
19	24	46%	54%	64 (39-72)	11 (8-14)	130 (113-169)	23 (14-26)	16 (10-24)	5 (21)
20	17	53%	78%	41 (29-50)	4 (3-10)	137 (80-154)	34 (26-45)	10 (7-18)	2 (22)
21	36	53%	21%	50 (32-79)	6 (3-15)	129 (105-140)	19 (10-29)	17 (13-18)	3 (16)
22	17	94%	47%	55 (33-70)	13 (3-15)	119 (84-140)	25 (12-34)	19 (14-25)	4 (24)
23	18	67%	64%	49 (33-69)	10 (3-15)	145 (112-156)	25 (21-32)	14 (10-17)	5 (28)
24	13	69%	56%	68 (48-80)	14 (7-15)	137 (119-165)	25 (19-27)	15 (12-20)	2 (22)
25	3	33%	100%	16	3	124	25	7	0
26	8	63%	80%	57 (34-67)	12 (4-14)	159 (113-179)	9 (4-34)	22 (16-29)	2 (40)
27	33	36%	58%	50 (41-57)	15 (12-15)	121 (103-140)	14 (9-21)	13 (9-16)	3 (25)
28	2	100%	100%	29 (17-40)	8 (8-8)	126 (143-149)	29 (20-38)	20 (19-21)	0
29	9	89%	50%	55 (39-66)	10 (5-15)	123 (72-172)	18 (12-58)	17 (12-22)	3 (38)
Average	15.6	59%	52%	48 (30-62) ǂ	10 (4-14) ǂ	124 (104-123) ǂ	24 (16-34) ǂ	14 (10-20) ǂ	2 (23)

Data presented for patients who developed MODS. ᵗ Median (IQR). Abbreviations = TBI: Traumatic Brain Injury; GCS: Glasgow Coma Scale; SBP: Systolic Blood Pressure; ISS: Injury Severity Score; APACHE II: Acute Physiology and Chronic Health Evaluation II. ORDIT site 2 enrolled two patients, neither of which developed MODS and sites 17 and 25 only had one patient who developed MODS.

TABLE E3. ADMISSION CHARACTERISTICS AND OUTCOMES FOR PATIENTS WITH MODS IN QUARTILES OF CRYSTALLOID

Crystalloid Volume	**<1.5L**	**1.5 - 2.6L**	**2.6 - 3.9L**	**>3.9L**
	57	***64***	***52***	***72***
Age	45 (31-65)	49 (30-62)	48 (32-68)	46 (28-57)
Male (%)	42 (74)	47 (73)	42 (81)	50 (69)
Blunt (%)	50 (88)	60 (94)	48 (92)	62 (85)
First GCS	13 (5-15)	14 (6-15)	14 (5-14)	14 (7-15)
First SBP	127 (110-145)	123 (94-137)	127 (104-142)	126 (103-149)
Admission BD (mEq/L)	0 (-0.1-4.0)	0 (-0.4-6.9)	0.05 (-0.5-6.8)	2.1 (0.1-7.0)
CSL L/24H (L)	0.25 (0-1)	2 (1.7-2.2)	2.9 (2.6-3.3)	5.5 (4.9-6.0)**
RBC units/24H	4 (1-6)	5 (2-7)	4 (2-6)	5 (2-6)
TBI (%)	26 (46)	25 (39)	21 (40)	27 (37)
ISS	25 (13-30)	26 (17-33)	25 (18-38)	26 (19-32)
APACHE II score	17 (10-18)	15 (11-22)	14 (10-18)	13 (9-21)
Outcomes:				
Mortality (%)	9 (16)	21 (33)	10 (19)	14 (19)
Ventilator days	3 (1-8)	3 (1-11)	4 (1-11)	5 (2-12)
CCLOS	6 (3-12)	7 (4-16)	10 (4-20)	13 (6-20)**
THLOS	23 (12-40)	25 (10-40)	25 (13-35)	33 (18-47)

Median (IQR) unless otherwise specified. **p<0.010 when comparing four groups, no comparisons reached p<0.05. Abbreviations = GCS: Glasgow Coma Scale; SBP: Systolic Blood Pressure; BD: Base Deficit; CSL: Crystalloid; RBC: Red Blood Cells; TBI: Traumatic Brain Injury; ISS: Injury Severity Score; APACHE II: Acute Physiology and Chronic Health Evaluation II; CCLOS: Critical Care Length of stay; THLOS: Total Hospital Length of stay.

Figure E1

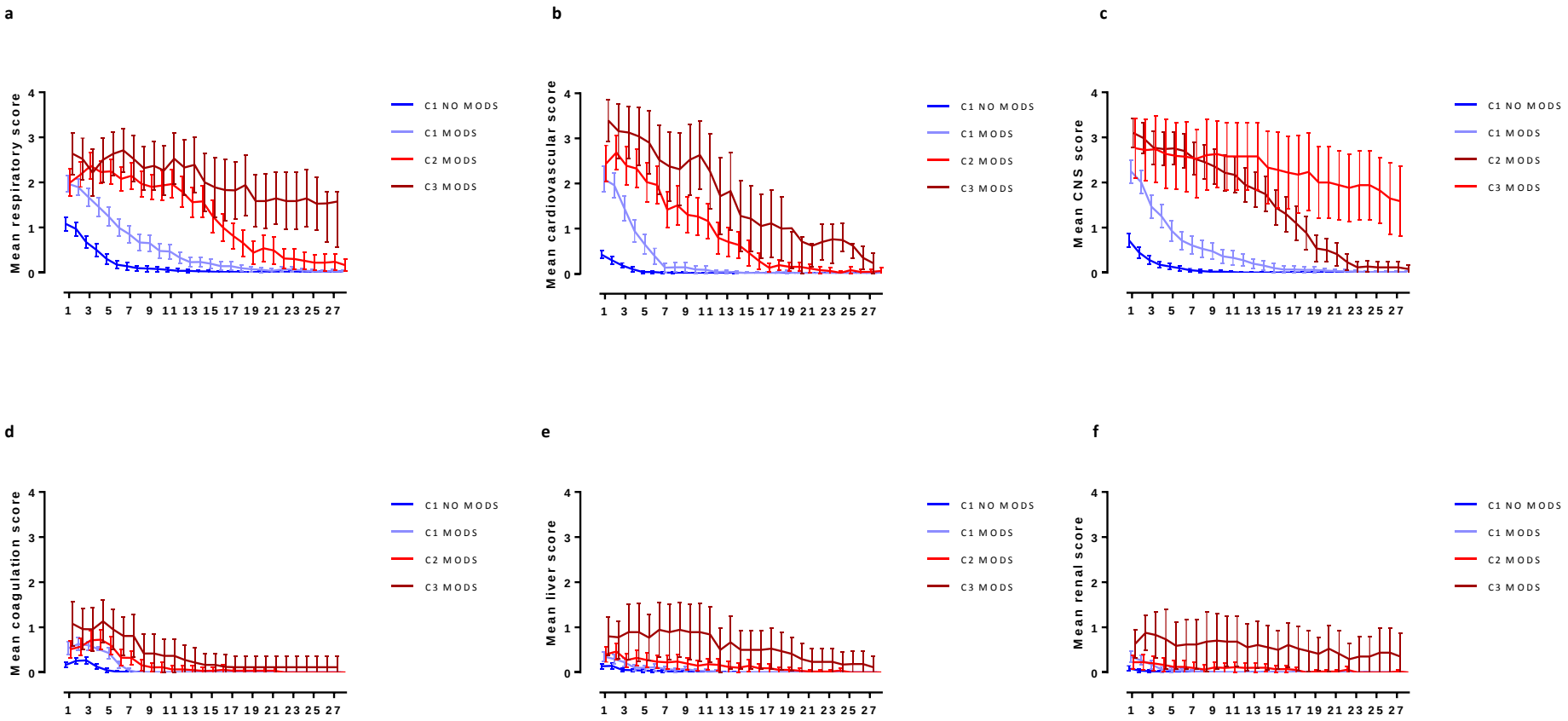
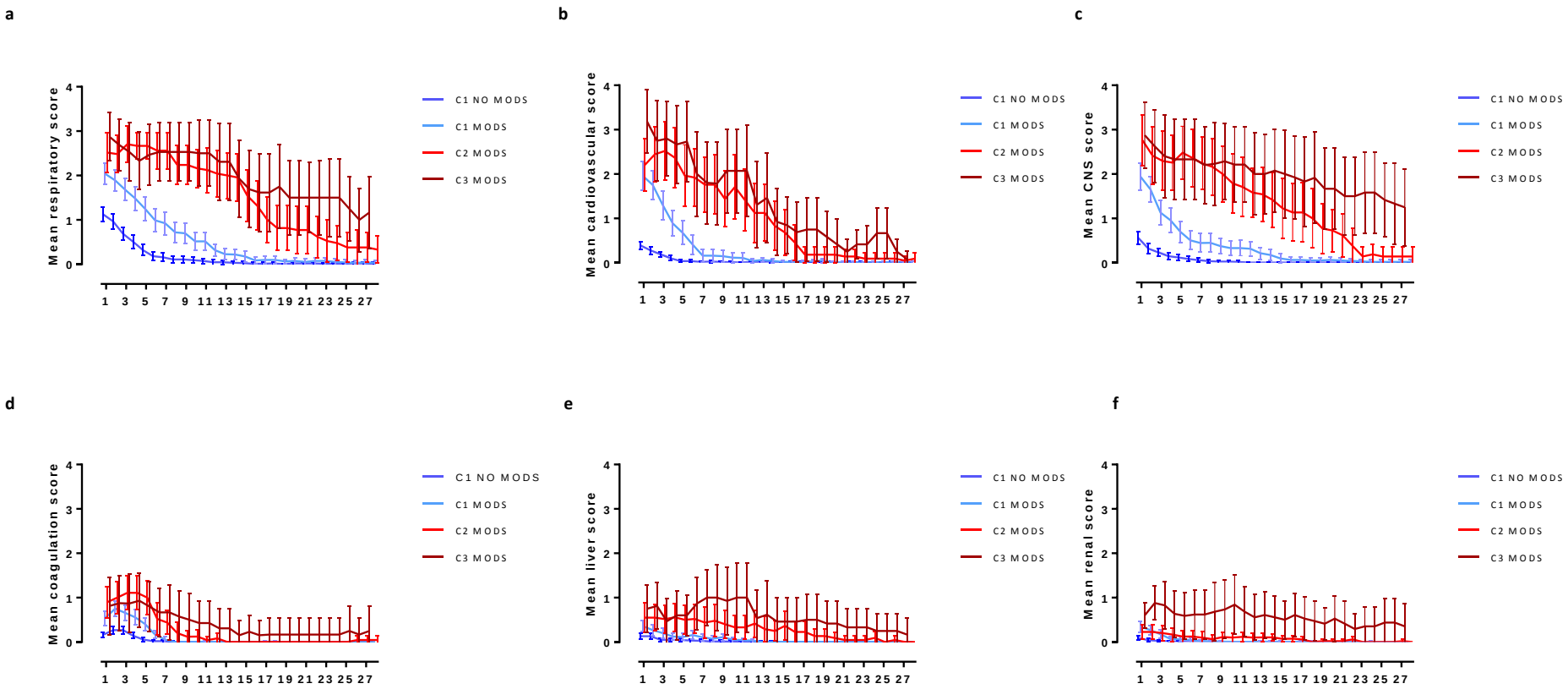

a
Mean respiratory score
b
Mean cardiovascular score
c
Mean CNS score
d
Mean coagulation score
e
Mean liver score
f
Mean renal score
C1 NO MODS
C1 MODS
C2 MODS
C3 MODS
0
1
2
3
4
1 3 5 7 9 11 13 15 17 19 21 23 25 27

Figure E2


a
Mean respiratory score
b
Mean cardiovascular score
c
Mean CNS score
d
Mean coagulation score
e
Mean liver score
f
Mean renal score
C1 NO MODS
C1 MODS
C2 MODS
C3 MODS
0
1
2
3
4
1 3 5 7 9 11 13 15 17 19 21 23 25 27

ONLINE DATA SUPPLEMENT FIGURE LEGENDS

Figure. E1. **Organ SOFA scores in *all patients*.** Line graphs show mean (95% CI) individual organ component SOFA scores for **a.** Respiratory, **b.** Cardiovascular, **c**. Central Nervous, **d.** Coagulation, **e**. Hepatic and **f**. Renal systems by day of hospital admission in patients within Cluster 1 (C1) No MODS, C1 MODS, Cluster 2 (C2) MODS and Cluster 3 (C3) MODS.

Figure. E2. **Organ SOFA scores in *patients without TBI*.** Line graphs show mean (95% CI) individual organ component SOFA scores for **a.** Respiratory, **b.** Cardiovascular, **c**. Central Nervous, **d.** Coagulation, **e**. Hepatic and **f**. Renal systems by day of hospital admission in patients within C1 No MODS, C1 MODS, C2 MODS and C3 MODS.