Superiority of serum cystatin-C over creatinine in prediction of long-term prognosis at discharge from ICU

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Running head: **Cystatin-c & post-ICU Mortality**

Abstract

Objective: Renal outcomes after critical illness are seldom assessed, despite strong correlation between chronic kidney disease (CKD) and survival. Outside hospital, renal dysfunction is more strongly associated with mortality when assessed by serum cystatin-c than by creatinine. The relationship between creatinine and longer-term mortality might be particularly weak in survivors of critical illness.

Design: Retrospective observational cohort study

Patients: In 3077 adult intensive care unit (ICU) survivors we compared ICU-discharge cystatin-c and creatinine and their association with one year mortality. Exclusions: death within 72h of ICU-discharge, ICU stay <24h, end-stage renal disease.

Interventions: None

Measurements and main results: During ICU admission serum cystatin-c and creatinine diverged so that by ICU discharge, almost twice as many patients had

glomerular filtration rate (GFR) <60ml/min/1.73m^2 when estimated from cystatin-c (eGFR-Cys-c) compared to creatinine (eGFR-Cr), 44% vs. 26%. In 743 patients without AKI, where ICU-discharge renal function should reflect ongoing baseline, discharge eGFR-Cr consistently over-estimated follow-up eGFR-Cr, while ICU-discharge eGFR-Cys-c well-matched follow-up CKD status. By one year 535 (17.4%) had died. In survival analysis adjusted for age, sex and comorbidity, cystatin-c was near-linearly associated with increased mortality, hazard ratio (HR)=1.78 (95% CI: 1.46-2.18), 75th versus 25th centile. Conversely, creatinine demonstrated a J-shaped relationship with mortality, so that in the majority of patients there was no significant association with survival, HR=1.03 (0.87-1.2), 75th vs. 25th centile. After adjustment for both creatinine and cystatin-c levels, higher discharge creatinine was then associated with lower long-term mortality.

Conclusions: In contrast to creatinine, cystatin-c consistently associated with long-term mortality, identifying patients at both high and low risk, and better correlated with follow-up renal function. Conversely, lower creatinine relative to cystatin-c appeared to confer adverse prognosis, confounding creatinine interpretation in isolation. Cystatin-c warrants further investigation as a more meaningful measure of renal function after critical illness.

Introduction

Acute kidney injury (AKI) increases risk of development or progression of chronic kidney disease (CKD) after critical illness(1, 2). CKD is associated with long-term risk of cardiovascular morbidity, end-stage renal disease (ESRD) and short- and long-term risk of death(3-6). Despite these important associations, survivors of critical illness with AKI rarely receive nephrology follow-up(7).

Assessment of renal function in survivors of critical illness requires tests of renal function that accurately reflect risk of long-term adverse outcomes. The endogenous biomarkers of renal function, creatinine and cystatin-c, both indirectly assess glomerular filtration rate (GFR)(8). While creatinine is standard, cystatin-c has limited uptake worldwide, despite potential superiority in prognostication of patients with CKD(9). Furthermore, interpretation of serum creatinine in intensive care survivors may be confounded by decreased creatinine generation(10, 11), thought to be a consequence sustained muscle wasting observed in critical illness. This effect is doubly confounding as muscle wasting is itself associated with adverse patient outcomes(12).

Cystatin-c is produced in nucleated cells and less confounded by acute and chronic illness, changes in diet and decreased muscle mass(13). In patients with CKD, estimated GFR (eGFR) based on cystatin-c better predicts mortality than eGFR based on creatinine which demonstrates a J-shaped relationship with risk of death(9). However, the relationship between cystatin-c and longer-term survival has not been compared to that of creatinine in the critically ill.

Accordingly, we examined seven years of patient data from a major teaching hospital intensive care unit (ICU) where both serum creatinine and cystatin-c are routinely measured. We hypothesized that, as a more accurate reflection of underlying renal function, cystatin-c would be strongly associated with long-term risk of death after ICU-discharge while serum creatinine might perform comparatively poorly.

Materials and methods

Study design

This cohort study was conducted in the multidisciplinary ICU at the Karolinska University Hospital Solna, Sweden: a 13-bed unit with approximately 1000 admissions yearly. The Stockholm Regional Ethics Committee approved the study, waiving informed consent due to retrospective observational nature of the study.

Inclusion and exclusion criteria

We screened all ICU patients admitted between October 2006 and December 2013. During this period, we only considered a patient's first ICU-admissions of >24h. We excluded deaths in-ICU or within three days of ICU-discharge, patients lacking linkage to mortality data, any patients with ESRD prior to ICU-admission or new ESRD with a chronic dialysis commencement date within 14 days of ICU-discharge. Lastly, we excluded patients lacking cystatin-c measurement near ICU-discharge (up to one-day prior or two days after ICU-discharge date).

Laboratory testing

Cystatin-c was determined with a turbidimetric method (Gentian Cystatin-c UDR-Kit for Beckman-Coulter Synchron and UniCel Systems, Ref A52761). Creatinine was determined with a modified Jaffe method (CREm, Creatinin, Ref 472525). We calculated eGFR for both markers using CKD-EPI(14).

Data collection

Patients were monitored using the patient database management system Clinisoft® GE, USA. From hospital electronic health records (EHR), (Take Care®**,** CompuGroup Medical, Germany) we linked diagnosis data from the index admission and prior clinical encounters with ICD-10 coding for assessment of comorbidities and calculation of Charlson Comorbidity Index, Quan modification (CCI)(15, 16). Linkage to EHR laboratory information before and after ICU-admission allowed assessment of pre-morbid, hospital discharge and follow-up creatinine. AKI was defined by the KDIGO criteria(17) as a 1.5 fold increase in serum creatinine from baseline during ICU-admission or an absolute 0.3mg/dl increase over a ≤48h period. Baseline creatinine was defined as the last value from 365 days to 7 days prior to hospital admission, or if unavailable the value closest to the admission value. Follow-up creatinine was the most recent value available from 30 days to one year after hospital discharge. Swedish resident registration number (18) allowed identification of date of all deaths. Linkage with the Swedish Renal Registry (SRR) allowed identification of patients with ESRD/time of first chronic dialysis.

Statistical analyses

Statistical analysis was performed using R Development Core Team R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org using the packages *Survival, SmoothHR, icd and rms*. Continuous variables are presented as median with interquartile range. Univariable comparisons were performed using the Wilcoxon Rank Sum Test, the Wilcoxon Signed-Rank Test and Fisher's Exact Test for continuous, paired continuous and binary data. Unadjusted survival data was stratified by quartiles of creatinine or cystatin-c and plotted as a Kaplan-Meier estimator and compared using the log-rank test. A two-tailed p-value of <0.05 was considered statistically significant.

Multivariable modelling

To assess the independent effect of renal filtration markers on survival in the year after hospital discharge multi-variable Cox proportional-hazard survival models were developed. To avoid concern regarding accuracy of eGFR equations in the ICU population we modeled the relationship between absolute creatinine or cystatin-c and mortality. We included age, sex, and comorbidity as covariates in our multivariable survival model as baseline factors likely to be associated with post ICU-survival and/or with renal function. In previous analyses of ICU survivors, comorbidity index was a stronger predictor of long term mortality than ICU-admission severity scoring (calibrated to short term risk of death)(19). To best illustrate the influence of AKI on the association of the filtration markers on survival we repeated analyses considering only AKI or non-AKI patients. In all models, we tested the proportional-hazards assumption by correlating the corresponding set of scaled Schoenfeld residuals with a Kaplan-Meier estimate of the survival function and non-proportional covariates

were handled by stratification for that variable. Based on general population data we hypothesized that creatinine or cystatin-c would be non-linearly related to risk of death; accordingly, these variables were fitted to a penalized spline. The degree of curve smoothing in the final model was determined by an algorithm based on minimization of Akaike's Information Criterion (AIC). Finally, we included creatinine and cystatin-c in a single age, sex and comorbidity adjusted multivariable model to explore the additive effects of these markers in combination.

Results

Demographics

After exclusions, 3077 survivors were included for primary analysis (Supplement Figure S1). By 90 days after ICU-discharge 318 died (10.3%) rising to 536 (17.4%) at one year. Nine patients developed new ESRD in the year after ICU-discharge. Non-survivors were older, had greater comorbidity, higher SAPS3 score, more often developed AKI and required RRT. Patients dying in the year after ICU-discharge had higher admission, peak and ICU-discharge creatinine than long-term survivors but these differences were more marked for cystatin-c at all time-points (Table 1). Importantly, while creatinine fell, from ICU-admission to discharge, cystatin-c rose over the same period (Table 1).

Renal function markers and mortality after ICU-discharge

Cystatin-c and creatinine at ICU-discharge differed distinctly in their association with mortality over the next 90 and 365 days (Table 2). The lowest cystatin-c quartile defined a low-risk population with a 5.6% one year mortality, compared to 13.6% in the lowest creatinine quartile. Overall, rates of death were well separated with increasing rates of death between quartiles of discharge cystatin-c whilst for creatinine only the upper quartile was separated (Figure 1).

Multi-variable survival analysis

To detect non-linear relationship between filtration markers and mortality risk, creatinine and cystatin-c were fitted to penalized splines in a multivariable survival model including sex, stratified for age and comorbidity index. Increasing cystatin-c

was near-linearly related to increasing HR for death; conversely creatinine demonstrated a J-shaped relationship (Figure 2). These relationships persisted when patients with or without AKI were considered separately (Figure S2). Considering both creatinine and cystatin-c together in a new multivariable model including age sex and comorbidity, increasing cystatin-c remained strongly associated with increasing HR for death, however, higher creatinine was then associated with *lower* hazard of death at all creatinine levels (Figure 3).

Relationship between cystatin-c and creatinine based estimates of GFR

Median eGFR at ICU-discharge based on creatinine was greater than using cystatin-c (92 vs. 68ml/min/1.73m^2, p<0.001). Using cystatin-c for eGFR identified 1362 (44%) patients <60ml/min/1.73m^2 at ICU-discharge compared to only 794 (26%) using creatinine based eGFR. Despite a substantially larger population with low eGFR, there was similar mortality in the cystatin-c group with eGFR<60 compared to that defined by creatinine eGFR (cystatin-c: 386/1362, 28% vs. creatinine: 233/794, 29%, (Table S1).

We examined cystatin-c/creatinine divergence during ICU-stay by comparing ratio of creatinine to cystatin-c eGFR for different durations of ICU-admission (Figure S3). In admissions lasting 1-2 days, the median ratio was 1.01 (IQR: 0.87-1.24). However, with longer admissions eGFR by creatinine was consistently greater than eGFR cystatin-c. For ICU-admissions of >20 days values of eGFR (creatinine) were a median of 2.1 (IQR 1.7-2.8) fold greater than corresponding eGFR (cystatin-c). Finally, to illustrate the timing of changes in creatinine and cystatin-c after ICU

admission we examined changes in creatinine, cystatin-c and C-reactive protein (CRP) over the first seven days of ICU admission and at ICU discharge in a subset of 516 patients with ICU admissions of ≥7 days. In this analysis creatinine progressively fell while at the same time cystatin-c rose (Fig S4). During this period, CRP had a biphasic profile and did not correlate with the two endogenous renal filtration markers.

To explore the discrepancy of cystatin-c and creatinine at ICU-discharge we considered 743 patients without AKI in the ICU (where ICU-discharge renal function would be expected to be similar to follow-up) who had a creatinine measurement in the 30-365 days after discharge and survived to 1 year. In this group, we compared cystatin-c and creatinine eGFR at ICU-discharge against follow-up creatinine eGFR (at a median of 267 days (IQR 145-334) after hospital discharge). GFR based on cystatin-c better agreed with CKD categorization at follow-up, particularly in the GFR range 30-60. In contrast, discharge creatinine eGFR over-estimated follow-up GFR in all CKD categories (Figure S5, Table S2).

Discussion

Interpretation of findings

In a large critically ill adult patient population we found cystatin-c was near linearly associated with age and comorbidity-adjusted 90- and 365-day mortality. In contrast, creatinine was unable to discriminate low-risk patients, showing a flattened J-shaped relationship with risk of death. While in the majority of patients discharge creatinine

that was not significantly predictive of risk of death, across the full range of measured values, cystatin-c provided prognostic information.

In line with these findings, during ICU-admission on average creatinine fell, while in the same patient group cystatin-c rose, resulting in a striking 24ml/min/1.73m^2 median difference in eGFR based on cystatin-c vs. creatinine at ICU-discharge. Both markers supposedly reflect true underlying GFR, but clearly one, or both, fail to do so in this setting. If excretion of markers is similarly affected by renal function, the generation rate of one or both must be substantially altered during critical illness. Given that cystatin-c is robustly related to risk of death while creatinine is not, we believe our findings are most compatible with cystatin-c better reflecting underlying renal function. This conclusion is supported by the observation that, in non-AKI-patients, where underlying GFR would not be expected to change markedly during convalescence, ICU-discharge cystatin-c eGFR better correlated with follow-up CKD-status than creatinine eGFR (Figure S4, Table S2).

Acute and chronic reduction in creatinine generation with muscle wasting may explain an inability to associate lower discharge creatinine with better prognosis, an interpretation strengthened by the finding that, for short ICU-admissions, cystatin-c and creatinine eGFR at discharge are similar. With longer ICU stays eGFR (creatinine) tends to be increasingly higher than eGFR (cystatin-c), a finding compatible with progressive muscle wasting during prolonged critical illness (Figure S3). Finally, when both markers were considered together in a survival model, increasing cystatin-c remained strongly associated with mortality, however,

increasing creatinine then became consistently associated with lower mortality, potentially reflecting lower mortality in patients with less muscle wasting (Figure 3).

Relation to previous studies

Assessment of renal function using creatinine has been shown to be confounded by progressive creatinine reduction associated with critical illness(10, 11) and accounting for these reductions results in more than doubling of patients with potential CKD at ICU-discharge. Decreased creatinine excretion, paralleling decreased production has been demonstrated with prolonged critical illness(11). In contrast, several studies suggest that cystatin-c outperforms creatinine in ICU populations. In cardiovascular surgery, creatinine eGFR over-estimated iohexol measured-GFR whereas cystatin-c eGFR well-matched(20). Similarly, in a general ICU patients, cystatin-c-estimated GFR was significantly lower than creatinine eGFR(21). Reductions in creatinine generation have been demonstrated in an animal model of sepsis(22); notably, in this model cystatin-c production was not increased(23), suggesting any cystatin-c elevation during critical illness is likely to reflect reduced renal clearance. The hypothesis that cystatin c production rises as an inflammatory response has also not been supported by previous comparisons to inflammatory markers in humans(24), while, in our study, elevation in cystatin-c was progressive and persistent, despite resolution of systemic inflammation as indicated by fall in CRP (Fig S4).

We have previously demonstrated an association between cystatin-c but not creatinine short term ICU mortality in a small sample of patients(25). This study

extends those findings, demonstrating a consistent association between cystatin-c at ICU-discharge and longer-term mortality in a much larger population critically ill patients with and without AKI. Cystatin-c has also been shown to better-correlate with mortality in settings where creatinine values may be confounded by premorbid condition, including vascular surgery patients(26), HIV patients(27), liver transplant recipients(28) and in acute heart failure(29); as well as in the general population and patients with CKD(9).

Study Implications

Consequences of AKI include increased long-term risk of death, cardiovascular events, development of CKD, and ESRD(5, 6). Incomplete recovery from severe AKI is a well-recognized pathway to persistent and progressive CKD (30), but recent studies suggest that apparently completely recovered AKI remains associated with a subsequent risk of CKD and death(5, 31). Importantly, the majority of such patients do not receive kidney-directed follow-up. Our findings suggest that a substantial number of these patients could have significant renal dysfunction undetected by creatinine. Notably, in this study, the where ICU-discharge renal function would be expected to be similar to follow-up 628 “extra” patients identified with an ICU-discharge eGFR of <60 by cystatin-c, but not creatinine, had similar risk of death to patients with eGFR <60 by creatinine based calculation, suggesting cystatin is correctly classifying patients at increased risk. Cystatin-c has the potential to target a larger group of high-risk patients for specialist follow-up that might improve outcomes(32) and also to accurately identify a group of low risk patients.

Strengths and weaknesses

This study is the largest comparison between creatinine and cystatin-c as markers of renal function in ICU patients. High-resolution data-linkage allowed us to precisely identify the presence and severity of AKI in the ICU, to collect detailed comorbidity data, to remove chronic dialysis patients and to obtain accurate all-cause mortality (33).

A weakness of this study is lack of gold standard GFR. Despite circumstantial evidence that our results reflect limitations of serum creatinine as a GFR biomarker after critical illness, without reliable measurement of GFR we cannot exclude the presence of increased cystatin-c production that is independently associated with increased mortality(9, 34). However, evidence suggests that such increases are not observed in clinical or experimental sepsis(23, 35). Cystatin-c measurements were confined to the ICU, i.e. the time-point of comparison, at ICU-discharge, was one of only relative clinical stability and renal recovery after AKI may still be occurring at this point. Our primary analysis concentrated on absolute values of creatinine and cystatin-c. To compare predicted renal function from these markers we used eGFR in secondary analyses, eGFR equations are unlikely to be accurate in the critically ill, however the purpose of such comparison is only to better-demonstrate the discrepancy between the markers and their agreement with baseline and follow-up. Finally, being a single center study, our findings would need confirmation in groups of differing socio-economic background and diverse ethnicity.

Conclusions

In a large population of critically ill patients, cystatin-c progressively rose during ICU treatment while creatinine fell, despite both being markers of glomerular filtration. Levels of cystatin-c after critical illness were strongly associated with 90-day and one-year mortality both in AKI- and non-AKI-patients. Cystatin-c identified almost twice as many patients as having clinically significant renal dysfunction at ICU-discharge and was superior in CKD categorization in the year following the critical illness. Conversely, creatinine was poorly related to risk of death and, in isolation, had little value as a prognostic marker in the majority of patients. Cystatin-c is likely to be the superior renal functional marker in survivors of major illness and should be investigated as a prognostic marker for patients at risk of CKD for follow-up and targeted intervention.

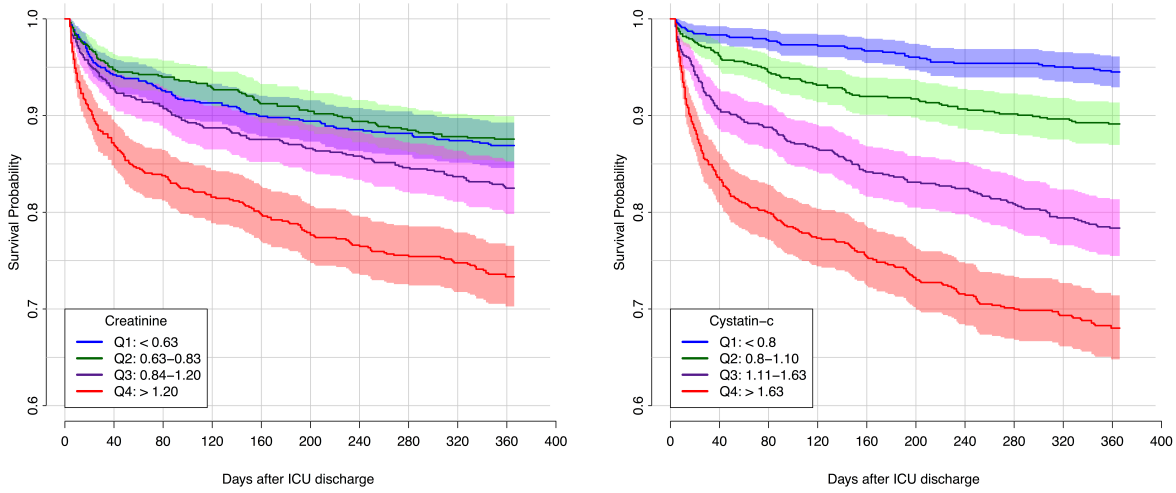

Figure 1. Crude mortality in the year after ICU-discharge stratified by quartiles of Creatinine or Cystatin-c at ICU-discharge.

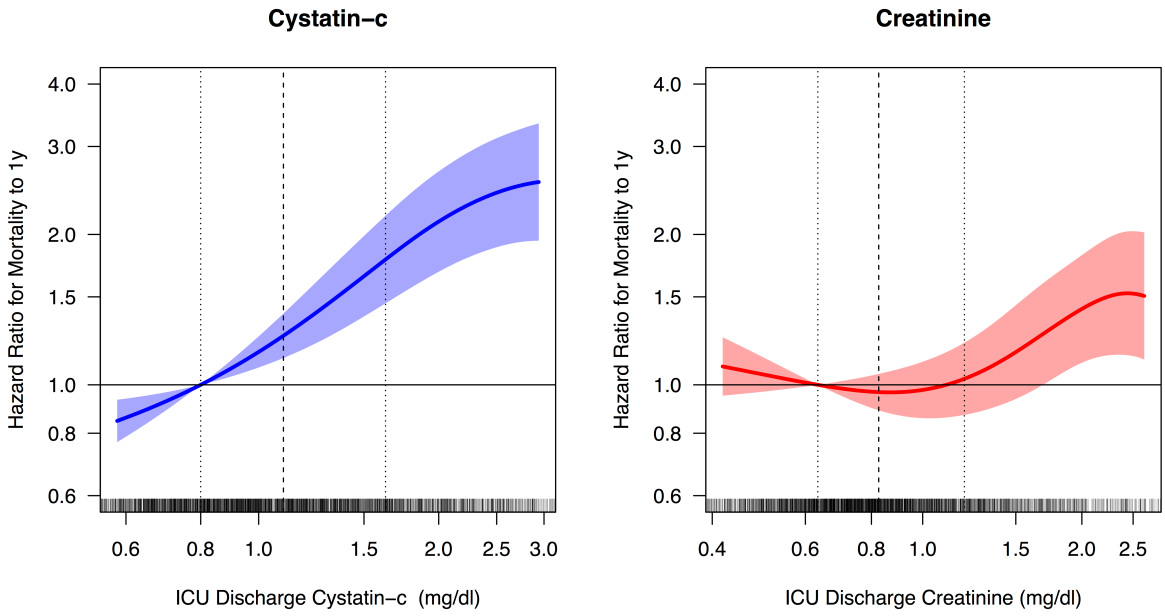

Figure 2. Age and Sex adjusted Hazard Ratios for survival in the year after ICU-discharge fitted with penalized spline regression for ICU-discharge Creatinine and Cystatin-c. Stratified Cox-Model (Strata: Co-morbidity Index category (0, 1-2, 3-4, 5-6, >6) and octiles of age). Values plotted from the 5th to 95th centiles the predictor variable and distribution of values within this range is marked above the x-axis. Reference is 25th centile value set to HR=1, 25th, 50th & 75% centiles are marked with vertical lines.

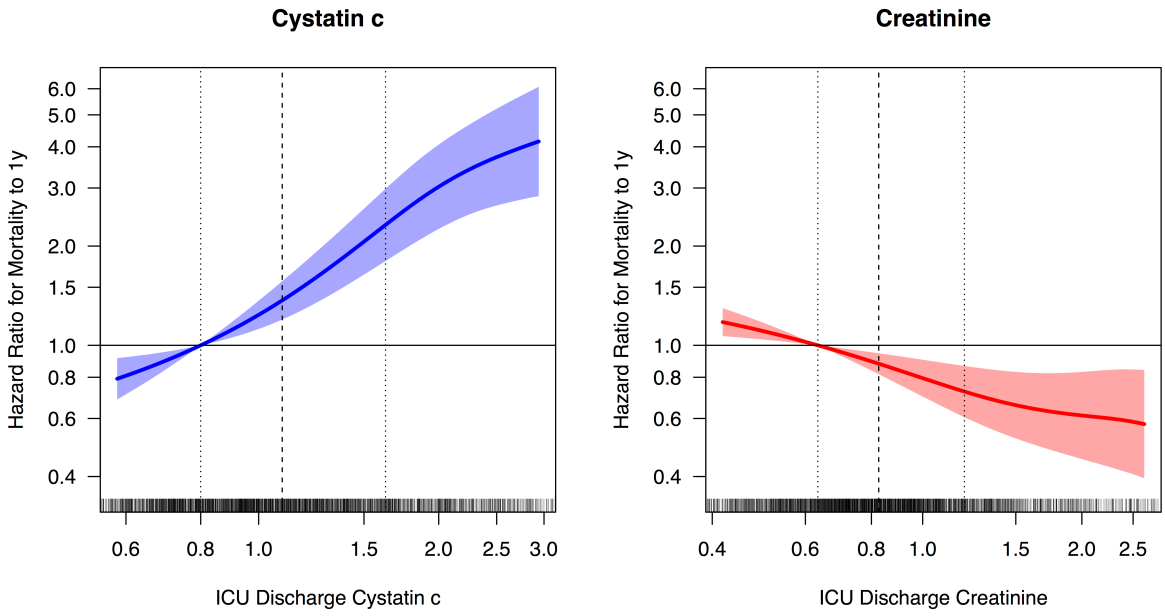

Figure 3. Including Cystatin-c and Creatinine together in a single Cox-Proportional Hazard survival model, Age and Sex adjusted Hazard Ratios for survival in the year after ICU-discharge fitted with penalized spline regression for ICU-discharge Creatinine adjusted for Cystatin-c and Cystatin-c adjusted for Creatinine. Stratified Cox-Model (Strata: Co-morbidity Index category (0, 1-2, 3-4, 5-6, >6) and octiles of age). Values plotted from the 5th to 95th centiles the predictor variable and distribution of values within this range is marked above the x-axis. Reference is 25th centile value set to HR=1, 25th, 50th & 75% centiles are marked with vertical lines.

	All Patients		Survived 1 year		Died by 1 year	
	(No. or median)	IQR or %	(No. or median)	IQR or %	(No. or median)	IQR or %
Number	3077	100%	2542	82.6%	535	17.4%
Age	59	41-70	56	38-68	69	60-76
Male Sex	1899	61.7%	1559	61.3%	340	63.4%
ICU LOS (h)	58	34-120	58	33-119	62	37-125
SAPS-3*	37	26-50	35	24-48	47	36-57
Medical	1348	43.8%	1039	40.9%	309	57.8%
Surgical	959	31.2%	776	30.5%	183	34.2%
Trauma	770	25.0%	727	28.6%	43	8.0%
Infection (Primary diagnosis)	704	22.8%	520	20.5%	184	34.4%
Closest to ICU Admission Creatinine	0.98	0.74-1.41	0.96	0.74-1.38	1.14	0.80-1.73
Closest to ICU Admission Cystatin-c*	1.01	0.75-1.53	0.94	0.72-1.38	1.36	1.02-1.93
Peak Creatinine	1.06	0.79-1.66	1.03	0.77-1.56	1.30	0.87-2.15
Peak Cystatin-c	1.20	0.83-1.93	1.11	0.80-1.76	1.69	1.19-2.52
Discharge Creatinine	0.83	0.63-1.20	0.80	0.62-1.13	1.02	0.69-1.57
Discharge Cystatin-c	1.10	0.80-1.63	1.01	0.77-1.48	1.57	1.12-2.16
Discharge eGFR (Cre)	92	58-112	95	65-115	70	41-96
Discharge eGFR (Cys-c)	68	37-105	76	44-109	40	26-64
RRT in ICU	238	7.7%	177	7.0%	61	11.4%

Table 1. Demographics and renal filtration markers in concentrations in survivors and non-survivors

* Values available in 3013 patients for SAPS3, 3070 for closest to admission cystatin-c.

	Unadjusted Post-ICU Survival by Quartile of Cystatin-c or Creatinine				Adjusted HR 75th relative to 25th centile
	Q1	Q2	Q3	Q4	
Cystatin-c					
Values (mg/L)	0.20-0.80	0.80-1.10	1.10-1.63	1.63-8.48	1.63 vs. 0.80
90-day mortality	2.6%	6.2%	11.8%	21.0%	2.23 (1.63-3.02)
365-day mortality	5.6%	11.0%	21.2%	32.0%	1.78 (1.46-2.18)
Creatinine					
Values (µmol/L)	0.1-0.63	0.63-0.83	0.83-1.20	1.20-11.55	1.20 vs. 0.63
90-day mortality	8.4%	6.3%	9.9%	17.0%	1.09 (0.89-1.33)
365-day mortality	13.6%	12.4%	17.3%	26.7%	1.03 (0.87-1.21)

Table 2. Crude mortality and adjusted hazard ratios for death over 90day and one year follow up after critical illness associated with plasma cystatin-c and creatinine measurements near ICU-discharge

References

1. Kirwan CJ, Blunden MJ, Dobbie H, et al. Critically ill patients requiring acute renal replacement therapy are at an increased risk of long-term renal dysfunction, but rarely receive specialist nephrology follow-up. Nephron 2015;129(3):164-170.

2. Siew ED, Peterson JF, Eden SK, et al. Outpatient nephrology referral rates after acute kidney injury. J Am Soc Nephrol 2012;23(2):305-312.

3. Chawla LS, Amdur RL, Amodeo S, et al. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int 2011;79(12):1361-1369.

4. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney Int 2012;82(5):516-524.

5. Rimes-Stigare C, Frumento P, Bottai M, et al. Long-term mortality and risk factors for development of end-stage renal disease in critically ill patients with and without chronic kidney disease. Crit Care 2015;19(1):383.

6. Rimes-Stigare C, Frumento P, Bottai M, et al. Evolution of chronic renal impairment and long-term mortality after de novo acute kidney injury in the critically ill; a Swedish multi-centre cohort study. Crit Care 2015;19:221.

7. Schetz M, Gunst J, De Vlieger G, et al. Recovery from AKI in the critically ill: potential confounders in the evaluation. Intensive Care Med 2015;41(9):1648-1657.

8. Carlier M, Dumoulin A, Janssen A, et al. Comparison of different equations to assess glomerular filtration in critically ill patients. Intensive Care Med 2015;41(3):427-435.

9. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med 2013;369(10):932-943.

10. Prowle JR, Kolic I, Purdell-Lewis J, et al. Serum creatinine changes associated with critical illness and detection of persistent renal dysfunction after AKI. Clin J Am Soc Nephrol 2014;9(6):1015-1023.

11. Schetz M, Gunst J, Van den Berghe G. The impact of using estimated GFR versus creatinine clearance on the evaluation of recovery from acute kidney injury in the ICU. Intensive Care Med 2014;40(11):1709-1717.

12. Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. JAMA 2013;310(15):1591-1600.

13. Kashani KB, Frazee EN, Kukralova L, et al. Evaluating Muscle Mass by Using Markers of Kidney Function: Development of the Sarcopenia Index. Crit Care Med 2016.

14. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367(1):20-29.

15. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-383.

16. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173(6):676-682.

17. Mizuno T, Sato W, Ishikawa K, et al. KDIGO (Kidney Disease: Improving Global Outcomes) criteria could be a useful outcome predictor of cisplatin-induced acute kidney injury. Oncology 2012;82(6):354-359.

18. Lunde AS, Lundeborg S, Lettenstrom GS, et al. The person-number systems of Sweden, Norway, Denmark, and Israel. Vital Health Stat 2 1980(84):1-59.

19. Ho KM, Knuiman M, Finn J, et al. Estimating long-term survival of critically ill patients: the PREDICT model. PLoS One 2008;3(9):e3226.

20. Bronden B, Eyjolfsson A, Blomquist S, et al. Evaluation of cystatin C with iohexol clearance in cardiac surgery. Acta Anaesthesiol Scand 2011;55(2):196-202.

21. Lipcsey M, Furebring M, Rubertsson S, et al. Significant differences when using creatinine, modification of diet in renal disease, or cystatin C for estimating glomerular filtration rate in ICU patients. Ups J Med Sci 2011;116(1):39-46.

22. Doi K, Yuen PS, Eisner C, et al. Reduced production of creatinine limits its use as marker of kidney injury in sepsis. J Am Soc Nephrol 2009;20(6):1217-1221.

23. Leelahavanichkul A, Souza AC, Street JM, et al. Comparison of serum creatinine and serum cystatin C as biomarkers to detect sepsis-induced acute kidney injury and to predict mortality in CD-1 mice. Am J Physiol Renal Physiol 2014;307(8):F939-948.

24. Grubb A, Bjork J, Nyman U, et al. Cystatin C, a marker for successful aging and glomerular filtration rate, is not influenced by inflammation. Scand J Clin Lab Invest 2011;71(2):145-149.

25. Bell M, Granath F, Martensson J, et al. Cystatin C is correlated with mortality in patients with and without acute kidney injury. Nephrol Dial Transplant 2009;24(10):3096-3102.

26. Kim GS, Ko YG, Shin DH, et al. Elevated serum cystatin C level is an independent predictor of contrast-induced nephropathy and adverse outcomes in patients with peripheral artery disease undergoing endovascular therapy. Journal of vascular surgery 2015;61(5):1223-1230.

27. Yanagisawa N, Sasaki S, Suganuma A, et al. Comparison of cystatin C and creatinine to determine the incidence of composite adverse outcomes in HIV-infected individuals. J Infect Chemother 2015;21(2):84-89.

28. Allen AM, Kim WR, Larson JJ, et al. Serum Cystatin C as an Indicator of Renal Function and Mortality in Liver Transplant Recipients. Transplantation 2015;99(7):1431-1435.

29. Ruan ZB, Zhu L, Yin YG, et al. Cystatin C, N-terminal probrain natriuretic peptides and outcomes in acute heart failure with acute kidney injury in a 12-month follow-up: Insights into the cardiorenal syndrome. J Res Med Sci 2014;19(5):404-409.

30. Chawla LS, Eggers PW, Star RA, et al. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 2014;371(1):58-66.

31. Bucaloiu ID, Kirchner HL, Norfolk ER, et al. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. Kidney Int 2012;81(5):477-485.

32. Harel Z, Wald R, Bargman JM, et al. Nephrologist follow-up improves all-cause mortality of severe acute kidney injury survivors. Kidney Int 2013;83(5):901-908.

33. Johansson LA, Bjorkenstam C, Westerling R. Unexplained differences between hospital and mortality data indicated mistakes in death certification: an investigation of 1,094 deaths in Sweden during 1995. J Clin Epidemiol 2009;62(11):1202-1209.

34. Tangri N, Inker LA, Tighiouart H, et al. Filtration markers may have prognostic value independent of glomerular filtration rate. J Am Soc Nephrol 2012;23(2):351-359.

35. Martensson J, Martling CR, Oldner A, et al. Impact of sepsis on levels of plasma cystatin C in AKI and non-AKI patients. Nephrol Dial Transplant 2012;27(2):576-581.