

Early (6-hr median) Change in Serum Creatinine is Comparable to APACHE II Score as a Prognostic Indicator in Septic Shock: A Multicentre, Retrospective Cohort Study

Murdoch Leeies

University of Manitoba

Faisal Siddiqui

University of Manitoba

Dan Chateau

University of Manitoba

Ryan Zarychanski

CancerCare Manitoba

Daniel Feinstein

University of North Carolina System

Paul Ellis

University Health Network

Yaseen Arabi

King Saud bin Abdulaziz University for Health Sciences

Peter Dodek

University of British Columbia

Phil Dellinger

University of Medicine and Dentistry, New Jersey

Anand Kumar

akumar61@yahoo.com

University of Manitoba

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Abstract

Objective

Existing prognostic models for patients with sepsis and septic shock are limited by the requirement for lengthy observation, invasive catheterization, onerous calculations, and with some models, applicability only to specific sub-populations. The objective of this study was to examine the relationship between early changes (median 6 hrs post-hypotension documentation) in serum creatinine concentration and survival in patients who have septic shock in comparison to other predictive measures.

Design

Retrospective nested cohort study

Setting

Derivation (July 1, 1989 to June 30, 2007; n = 5410) and validation (July 1, 2007 to June 30, 2013; n = 4827) cohorts from the Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database

Methods

Change in serum creatinine concentration was assessed by categorizing creatinine levels at baseline, 3–9 (median 6) hours, and 20–28 (median 24) hours after onset of septic shock. The primary outcome was survival to hospital discharge. In the derivation cohort, correlates predictors of survival including trend in use of vasopressors, APACHE II score, age, platelet count, and serum lactate concentration were compared to change in serum creatinine (at first documentation of hypotension) via multivariate logistic regression. Sensitivity analyses were done in the validation cohort.

Main Results

In the derivation cohort, the change in serum creatinine concentration at 3–9 hours and 20–28 hours after onset of shock were associated with survival to hospital discharge (Wald $\chi^2 = 280.1$, $p < 0.001$ and $\chi^2 = 259.9$, $p < 0.001$, respectively). The strength of association between creatinine change at both time points and survival was comparable to those of vasopressor change (Wald $\chi^2 = 211.7$, $p < 0.001$) and APACHE II score (Wald $\chi^2 = 259.7$, $p < 0.001$) (both derived over the first 24 hours). Compared to the derivation cohort, the validation cohort demonstrated relationships that were consistent in direction and significance of effect.

Conclusions

A change in serum creatinine concentration 3–9 hrs after the onset of shock is an early prognostic measure in patients with septic shock comparable to APACHE II score and 24 hour vasopressor change.

INTRODUCTION

Sepsis is a syndrome of life-threatening organ dysfunction caused by a dysregulated host response to infection¹. Sepsis and septic shock rank among the leading causes of death for critically ill patients worldwide, accounting for approximately 15% of intensive care unit (ICU) admissions and the second most frequent cause of death in the ICU^{2,3}. Despite advances in early identification and supportive treatment, the burden of sepsis remains high. Contemporary epidemiologic studies of patients with septic shock conducted to inform the SEPSIS-3¹ septic shock definition found mean hospital mortality rates ranging from 35 to 54%⁴. The early phase of septic shock is a critical window where effective resuscitation and optimal application of antimicrobial therapy have the potential to preserve end organ function and improve outcomes^{5,6}.

Current mortality prediction scoring systems/algorithms for patients with sepsis and septic shock rely on data collected over at least 24 hours of ICU admission, require invasive catheterization or multi-step calculations, may depend on less than universally available laboratory tests and/or may not apply to all patient groups^{7–14}. A simple predictive index available early in a patient's course of care may help determine the need for more aggressive resuscitative strategies or provision of supplemental therapies and may be useful for early risk stratification for the purposes of clinical research. Serum creatinine concentration, in contrast to other laboratory tests such as C-reactive protein, procalcitonin, serum lactate and central venous oxygen saturation is readily available in resource-limited settings with only modest laboratory support.

Changes in serum creatinine concentration over the first 24 hours of septic shock are strongly associated with clinical outcome¹⁵. The purpose of this study was to determine whether early (3–9 hr) changes of serum creatinine concentration during septic shock are correlated with hospital survival, and to compare this correlation to that of other known prognostic measures such as initial serum lactate^{16,17}, 24 hour vasopressor change¹⁸ and Acute Physiology and Chronic Health Evaluation (APACHE II)¹¹ scores.

METHODS

Study Population

The Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database from which included cases were drawn has been previously described^{19,20}. We developed a derivation cohort for this analysis from the CATSS database that captured data on consecutive adult (> 18 years old) patients admitted with septic shock to 24 medical institutions in Canada, the United States, and Saudi Arabia between July 1, 1989 to June 30, 2007. The validation cohort consisted of patients admitted between July 1, 2007 and June 30, 2013. In addition to the original 24 derivation cohort sites, 6 additional North American sites contributed cases to the validation cohort. Potential cases for both cohorts were identified and screened

via internal ICU databases and/or *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD9-CM) coding strategies. Consecutive patients from discrete periods between July 1, 1989 and June 30, 2013 were included in the database if they meet the criteria for septic shock as defined by the 1991 American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) consensus conference guidelines²¹. Each site contributed a minimum of 100 cases. Not every site contributed data for every year of data collection. For the current study, we excluded cases without an initial serum creatinine concentration within 1 hr of documentation of sepsis-associated hypotension (baseline serum creatinine value). Patients with dialysis-dependent renal failure immediately before intensive care unit (ICU) admission were also excluded.

Trained research staff extracted data at all sites using a previously piloted and standardized data extraction template. All data extractors reviewed at least 100 patient charts and a minimum of 5% of all data was reviewed in duplicate by local principal investigators to confirm accuracy.

This research involved a retrospective analysis of de-identified medical record data under a waived consent protocol. The study was approved by the Health Research Ethics Board at the University of Manitoba and all participating institutions (see Appendix A). Research was performed in accordance with relevant guidelines/regulations including the Helsinki Declaration (<https://www.wma.net/policies-post/wma-declaration-of-helsinki/>)

Comparators

The primary independent variable of interest was *change in serum creatinine concentration* (Δ mmol/L) after the initial documentation of septic shock-associated hypotension. This variable was calculated as the difference between concentrations at baseline and at 3–9 hours and 20–28 hours after the first documented septic shock-associated hypotension. Serum creatinine changes were also assessed as percentage change from baseline. *Change in vasopressors* over 24 hours was an important secondary independent variable. *Change in vasopressors* over the first 24 hours of use was independently scored via majority assessment by 3 Critical Care specialists as either Group A) clearly decreasing (31.4%), Group B) uncertain/no clear directional change (31.1%) or Group C) clearly increasing (37.5%). Two major analyses were planned. In the first, all continuous prognostic variables were converted and assessed on a categorical basis (along with any intrinsically categorical variables). For comparison purposes, APACHE II and creatinine change values were categorized into three comparably-sized/proportioned groups based on the distribution of cases into the A, B and C groups in the change-in-vasopressor category (as above and Table 1). Additional comparably divided prognostic variables tested included age, admission serum creatinine, lactate and platelet counts. APACHE II scores were derived from the most aberrant values within 24 hours after septic shock diagnosis¹¹. In the second, all continuous variables were assessed as such (i.e. intrinsically categorical variables were necessarily excluded).

Table 1
– Group Categories for APACHE II, Vasopressors and Creatinine

Variable	Group A (N = 1699)	Group B (N = 1682)	Group C (N = 2029)
Vasopressor Change over 24 hrs	Decreased	Uncertain (no clear change)	Increased
Creatinine Change in 6 hrs	Decreased	Changed between	Increased
<i>Absolute Change</i>	> 10 µmol/L	-10 to + 9 µmol/L	> 9 µmol/L
<i>Relative Change</i>	> 7%	-7% to + 5%	> 5%
Creatinine Change in 24 hrs	Decreased	Changed between	Increased
<i>Absolute Change</i>	> 21 µmol/L	-21 to + 10 µmol/L	> 10 µmol/L
<i>Relative Change</i>	> 16%	-16% to + 8%	> 8%
APACHE II	≤ 20	21–28	≥ 29

Outcome Measures

The primary outcome variable was survival to hospital discharge. Additional potential early predictors of survival including change in vasopressor medication over the first 24 hours of shock, APACHE II score, age, admission creatinine, admission platelet count and admission serum lactate were assessed in comparison to each other.

Statistical Analysis

The strength of the association between prognostic variables including change in serum creatinine concentration and APACHE II score with survival to hospital discharge was quantified by the Wald χ^2 statistic taken from a series of multivariable logistic regression models that assessed the predictive power of four different measures of change in serum creatinine (3–9 hour versus 20–28 hour in both absolute and relative measures). Four separate models were run due to the considerable collinearity between the creatinine measures. For categorical variables divided into 3 subgroups (including decreasing, uncertain, or increasing creatinine), multivariable logistic regression models were built with the middle subgroup category acting as the referent in order to calculate an adjusted odds ratio (aOR) for survival for the upper and lower category of each variable. These potential predictors of survival were compared to each other using the χ^2 statistic from the model. Analyses were done on derivation (July 1, 1989 to June 30, 2007) and validation (July 1, 2007 to June 30, 2013) cohorts. All statistical analyses were conducted using SAS version 9.3 (Cary, NC USA) and used an α of 0.05. A Bonferroni correction for multiple comparisons was performed as appropriate.

RESULTS

Demographics

After applying our inclusion and exclusion criteria to the data set of 6512 septic shock cases to June 30, 2007, 5410 patients met inclusion criteria and were analyzed as the derivation cohort. The presence of dialysis-dependent renal failure at the time of occurrence of septic shock accounted for 450 excluded cases. Another 652 cases did not have serum creatinine values at the time of initial documentation of septic shock- associated hypotension. The 3–9 (median 6) hr and 20–28 (median 24) hr time points had creatinine values available for 4709 and 5241 cases respectively. APACHE scores and vasopressor change values over the first 24 hours were available in all cases.

Median serum creatinine concentration at admission with inter-quartile range (IQR) in the derivation cohort was 148 (94–232) mmol/L. Epidemiologic, physiologic and clinical characteristics of the derivation cohort are reported in Supplemental Tables 1 and 2.

Of all cases, 1699 were assessed by the panel as demonstrating a clear reduction in vasopressor dose over the first 24 hours of treatment (Group A, Table 1). In another 1682 cases, the trend was uncertain (Group B) and in a final group of 2029 cases, vasopressor doses were judged to be clearly increasing (Group C). Inter-rater reliability was excellent for all 3 possible pairs of the 3 assessors, with weighted kappa statistics greater than 0.90 for all three pairwise combinations (.9035, .9170, .9339). All disagreements were where one rater assessed an increase, or a decrease, while another assessed no change. There were no cases in which the assessment of each evaluator was entirely discordant with the others. Accordingly, categorical subgroups of comparable size/proportions (i.e. similar to those of the A, B and C groups of vasopressor change) were created using absolute and relative changes in the 3–9 hr and 20–28 hr creatinine values. Similar divisions were created for APACHE II scores. The cutoff values are shown in Table 1. In addition, divisions of comparable size were also generated for age as well as admission creatinine, lactate and blood platelet count.

The same analytic approach was used for the validation cohort. This cohort was composed of 5933 septic shock patients of which 1106 were excluded due to either the existence of ongoing renal dialysis before the occurrence of septic shock or lack of key creatinine results at the time of shock. In total, 4827 patients were used for analysis (Supplemental Tables 3 and 4).

Outcomes

In the derivation cohort, all assessed continuous variables (Supplemental Table 5) demonstrated a significant relationship with mortality. For platelet count, progressive decreases from baseline values were associated with increased risk of mortality. For age, APACHE II score, admission serum creatinine and lactate and changes in serum creatinine (absolute value and increase from baseline creatinine), higher values were associated with increased risk of mortality. The relationship between relative

(percent) changes in serum creatinine from baseline (i.e. time of initial documentation of septic shock-associated hypotension) to 3–9 hr later and hospital survival was highly significant ($p < 0.0001$; Fig. 1).

Categorical variables (each divided into comparably proportioned A, B and C groups) were tested to assess their relationship to survival (Supplemental Table 6, cutoff values displayed in Figs. 2 and 3). All tested categorical variables were associated with outcome. In particular, change in serum creatinine at 3–9 hours and 20–28 hours after onset of hypotension associated with septic shock was strongly correlated with the probability of survival to hospital discharge (Wald $\chi^2 = 280.1$, $p < 0.001$ and $\chi^2 = 259.9$, $p < 0.001$, respectively). Vasopressor change (Wald $\chi^2 = 211.7$, $p < 0.001$) was also strongly associated with outcome. Notably, the Wald χ^2 value, a measure of the strength of the relationship, was comparable for changes in serum creatinine concentration at both 3–9 hr and 20–28 hr and APACHE II score (Wald $\chi^2 = 259.7$, $p < 0.001$).

Survival to hospital discharge rates for Groups A and C (with group B as the reference group) for each explanatory variable are shown in Figs. 2 and 3. For the strongest relationships including 3–9 hr and 20–28 hr changes in serum creatinine concentration and APACHE II score, the odds ratio of survival ranged about 5–6 fold. For example, the odds ratio for percent change in serum creatinine concentration between initial hypotension and 3–6 h later was 0.46 (95% CI 0.37–0.57) for > 5% increase to 2.43 (95% CI 1.94–3.03) for > 7% decrease. As a comparison, the odds ratio for an APACHE II < 21 was 0.35 (95% CI 0.29–0.44) and for APACHE II > 28, the OR was 2.26 (95% CI 1.78–2.88).

Validation

Analyses on the validation cohort of patients with septic shock supported directional, statistically significant associations consistent with the primary analysis. (see Supplemental Tables 7 & 8). In addition, the APACHE and serum creatinine percent change (at median 6 hours) parameters from the derivation models were tested on the validation data set to determine the likelihood of correctly predicting survival. While APACHE II did perform better at correctly classifying survivors (65.6% compared to 50.0% for 6 hr creatinine), 6 hr % creatinine change was actually better at classifying those who would die in hospital (67.8% compare to 62.1% for APACHE). In other words, while 6 hr median percent creatinine change may have resulted in a larger proportion of false positives (i.e., survivors predicted to be deaths), this led to a greater sensitivity in predicting actual death.

DISCUSSION

The initial hours of severe sepsis and septic shock have been shown to be a critical window where appropriate volume resuscitation and rapid, targeted antimicrobials can reduce morbidity and mortality^{5,6,22}. As such the early identification, characterization and care of high risk patients with sepsis and septic shock requires ongoing rigorous study.

There are notable drawbacks to current prognostic methods. Prognostic scores in severe sepsis and septic shock are cumbersome, typically requiring assessment of multiple parameters measured over 24 hours of observation and may not apply equally to individual patients^{7-10,12-14,23}. Central venous oxygen saturation requires central venous access, a procedure with a small but measureable risk of morbidity²⁴ and also requires a blood gas analyzer which may not be available in poorly resourced settings. Accurate measurement of serum lactate levels requires either very rapid measurement or refrigeration in transport due to the ex-vivo leukocyte lactate production. In addition, as with blood gas analyzers, some poorly resourced sites may not be able to measure serum lactate concentration.. In contrast, assessment of serum creatinine concentration as a potentially strong prognostic marker in sepsis is appealing as it is used in routine clinical care and widely accessible, even in resource-limited settings.

We found that an increase in serum creatinine by as early as 3–9 (median 6) hours after documentation of hypotension in septic shock is strongly correlated with decreased survival to hospital discharge ($\chi^2 = 280.1$, $p < 0.001$). Notably, the strength of this correlation with outcome is similar to that for APACHE II score and change in dose of vasopressors, both of which require data collection over the first 24 hours of ICU admission. The change in serum creatinine at 20–28 (median 24) hours also correlated with outcome but was similar in strength to the correlation for the change at 3–9 (median 6) hours. A distinct change in serum creatinine early in the resuscitation of a septic patient might aid in guiding resuscitative strategies and adjunctive therapies, and could also serve as an early marker for risk stratification in clinical studies of septic shock.

Our findings are consistent with other mortality prediction models that correlate end organ dysfunction with prognosis^{7-10,25,26}. Acute kidney injury (AKI) in particular is associated with worse outcomes in septic shock²⁷⁻²⁹. Small increases in serum creatinine during the first 48 hours of a critical illness have been shown to be associated with increased mortality³⁰. An earlier analysis of the CATSS database demonstrated a survival benefit of with reversal of AKI by 24 hours¹⁵. This study furthers the characterization of renal function in septic shock by identifying a significant association between change in serum creatinine concentration and mortality at as early as 3–9 hours after first documentation of septic shock-associated hypotension.

This study was a retrospective analysis and subject to the inherent limitations of its design. It is possible that some univariate associations noted in Supplemental Table 5 were spurious and based on random sampling variation. However, statistical significance remained even with Bonferroni correction for multiple comparisons and with our validation cohort analysis. Known confounders were accounted for in the multivariate logistic regression model but unknown confounders may exert unrecognized influence in the model. One important variable not included is the volume and speed of initial fluid resuscitation. This was not included because the volume and speed of fluid resuscitation was not consistently collected (< 1/2 of all individual datasets). Extent of fluid resuscitation has the potential to alter outcome either adversely or favorably^{6,31-33}. Other data not available for model development include duration of sepsis before hypotension and potentially nephrotoxic medications used before (e.g. diuretics,

angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory agents, calcineurin inhibitors) or during (e.g. amphotericin B, aminoglycosides) the development of septic shock which could have an impact on the occurrence of renal failure.

This study also has a number of strengths. The broad database inclusion criteria in combination with the large sample size and multicentre nature of the study design also adds to the generalizability of the findings. Use of a temporally distinct validation cohort reinforces the potential applicability of our initial observation in the context of varying practice patterns over time.

Our study demonstrated that a decrease in serum creatinine over the first 3 to 9 hours of septic shock was a significant independent correlate of survival to hospital discharge. This is a novel observation. While we and others have shown a correlation between changes in serum creatinine or estimated creatinine clearance after 24 to 72 hours of septic shock, our observation of such a relationship as early as 3–9 (median 6) hrs after shock onset is unique. Perhaps more notable is the strength of this relationship as assessed by the relative Wald X^2 values. In multivariable analysis, the Wald X^2 value indicated that the 3–9 hr serum creatinine change had an equal or stronger relationship to survival than APACHE II score¹¹, 24 hour vasopressor change¹⁸ or admission serum lactate level^{16,17} each of which has been shown to be closely correlated with survival. Additional variables of age and 24 hour platelet count alterations were less strongly correlated with survival.

The change in serum creatinine 3–9 (median 6) hrs after the onset of shock may be the earliest and strongest easily available clinical indicator of outcome in patients with septic shock. The potential utility of such an early indicator of mortality risk relates to two areas. An early increase in serum creatinine in the initial presentation of septic shock may be driven by either under-resuscitation (with crystalloids, colloids or possibly with vasopressor medications) or by the occurrence of acute tubular necrosis, both of which are known to increase mortality risk. If the former, this early increase in serum creatinine may alert the treating physician to the need for further aggressive resuscitation, particularly with fluids. If the latter, complications of fixed renal injury and the potential need for renal support may both be anticipated in a timely manner. In addition, increases in serum creatinine as early as 3–9 (median 6) hours after presentation with septic shock-associated hypotension may be very useful for purposes of risk stratification in the context of clinical research. Unfortunately, most sepsis scoring systems require at least 24 hours of assessment for accurate prognostication^{8–11}. As a consequence, the opportunity for studies of early administration of experimental drugs into the high risk patients most likely to benefit may be problematic. The use of early changes in serum creatinine for risk stratification may be attractive as it is much less invasive than central venous oxygen saturations and generated much earlier in the disease process than most standard prognostic scores. Further prospective study is warranted to evaluate the use of this prognostic marker.

DECLARATIONS

Ethical Approval and Consent to Participate:

This study involved a retrospective analysis of de-identified medical record data. Ethical approval was obtained from the Institutional Review Board (IRB) / Ethics Committee of the University of Manitoba as the primary center and separately from each participating institution. A waiver of informed consent was granted by each board/committee due to the retrospective nature of the study and the use of anonymized data

Consent for Publication:

Not applicable.

Competing Interests:

None

Funding:

No funding was received for this study.

Author Contribution

AK had full access to all of the data in the study and takes responsibility for (is the guarantor of) the content of the manuscript, including the integrity of the data and analysis. All authors have contributed to this manuscript. ML, FS, DC, RZ, DF, PE, YA, PeD, PhD and AK made substantial contributions to the study's conception and design, data analysis and interpretation. AK and DC are responsible for the accuracy of the overall data analysis. All authors had a significant role in drafting or critically revising the manuscript for important intellectual content. AK was responsible for the final approval of the version to be published.

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Not applicable.

Data Availability

All data supporting the findings of this study are available within the paper and its Supplementary Information. The corresponding author will answer any requests for further data in accordance with institutional data sharing regulations.

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Figures

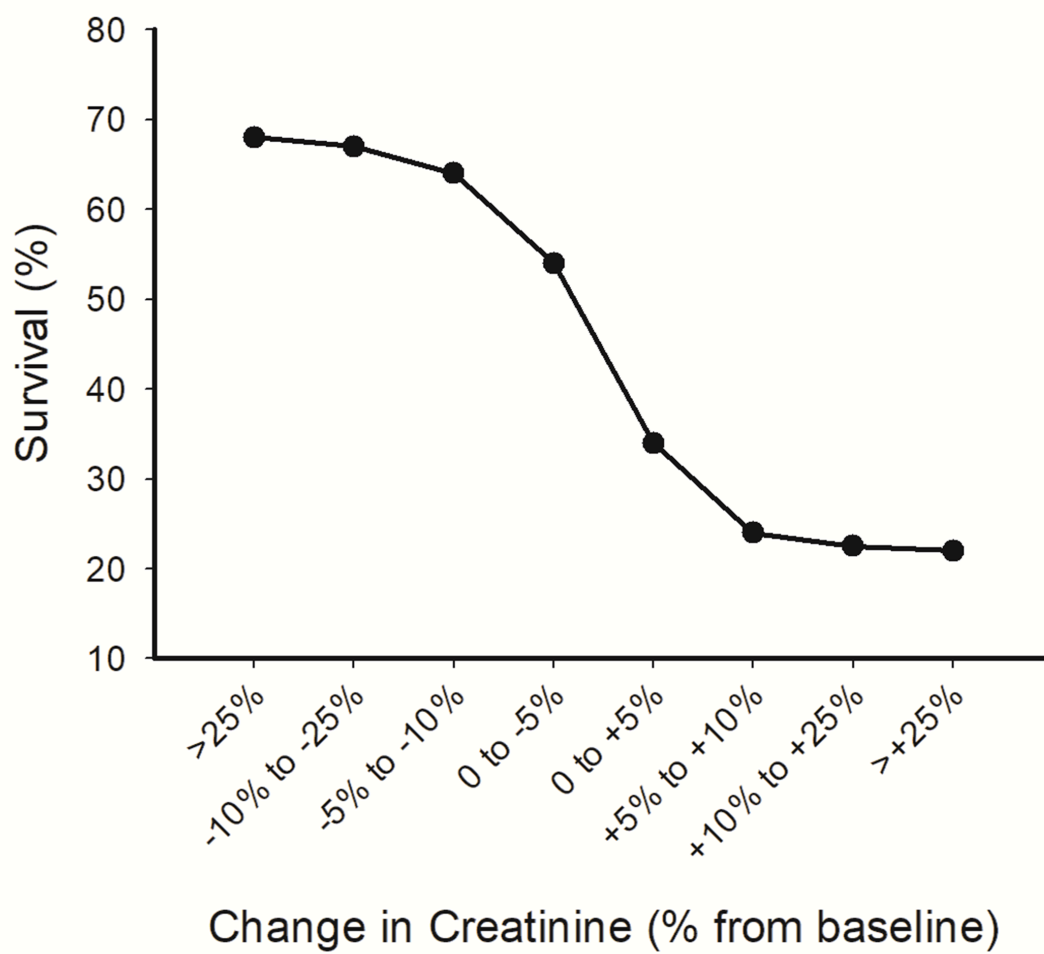


Figure 1

Survival (%) versus Early (3-9 hrs) Change (%) in Serum Creatinine

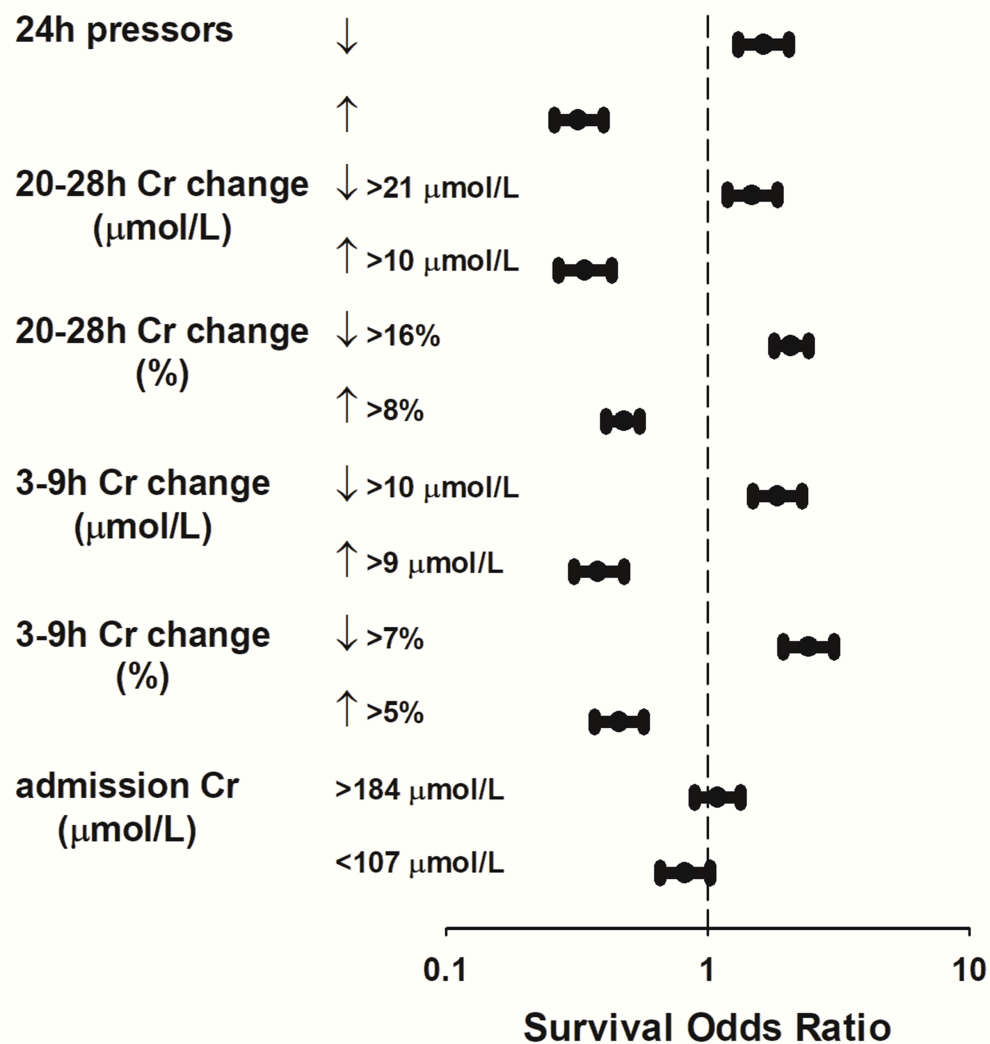


Figure 2

Odd Ratios For Changes In Vasopressor Dose And And Serum Creatinine Concentration As Predictors Of Hospital Survival

Cr, serum creatinine concentration

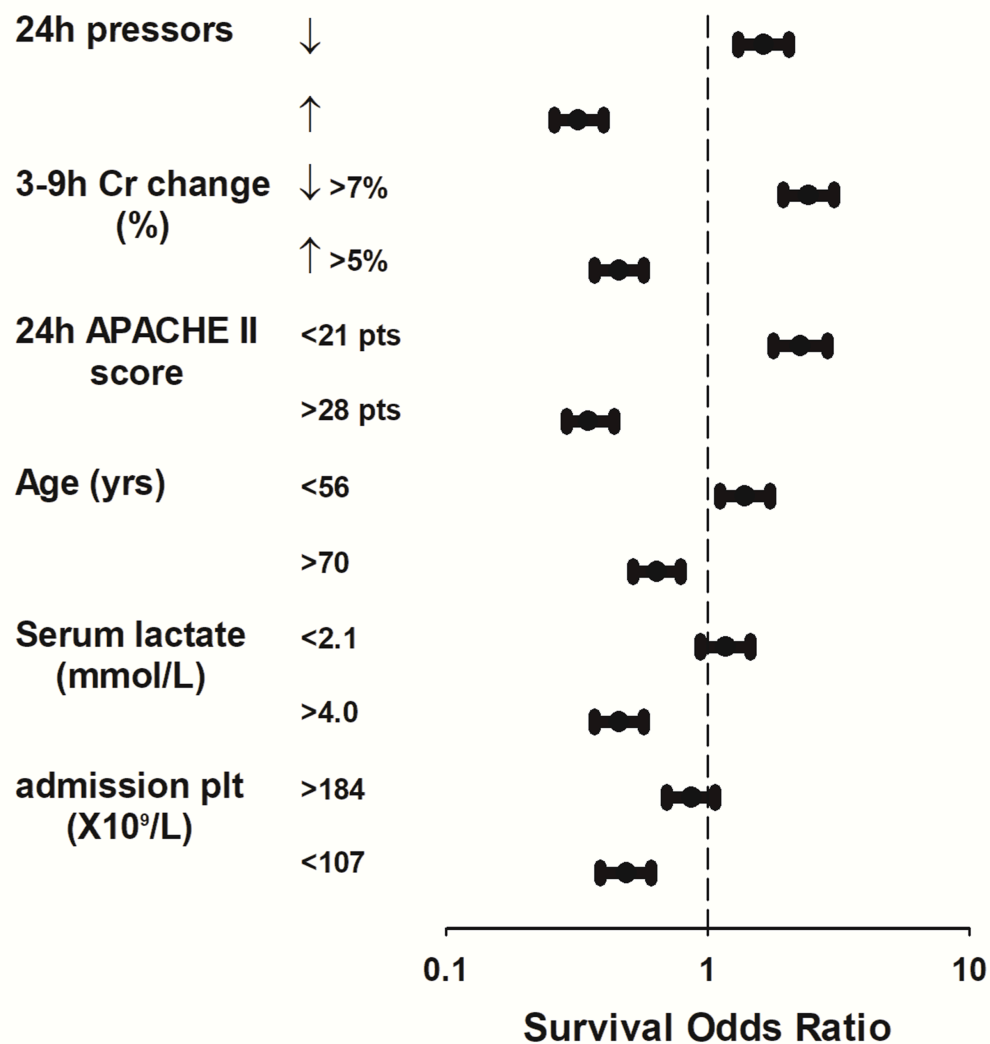


Figure 3

Survival Odd Ratios for All Assessed Variables

Cr, serum creatinine concentration

APACHE, Acute Physiology and Chronic Health Evaluation Score

pts, points

plts, platelets

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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