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ORIGINAL RESEARCH ARTICLE

Hepatic and Renal Biochemical Markers as Predictors of Mortality Among Critically Ill Systemic Inflammatory Response Syndrome Patients

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Abstract Systemic inflammatory response syndrome (SIRS) is a frequently encountered complication seen in intensive care unit patients and remains a common cause of mortality. Assessing prognosis of those becomes a priority and indeed we have various efficient scoring systems for the same. However they use enormous data and involve complex calculations for scoring. We intended to find a simple, inexpensive, accurate diagnostic tool of certain markers to predict mortality outcome among critically ill SIRS patients and to evaluate their efficiency in comparison to Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system. Eighty-seven patients were selected and general hepatic, renal and urinary investigations were done for them at 24 h of admission and were followed up for a period of 4 weeks from admission date to classify them as survivors and non-survivors. Twenty-one percent patients had succumbed to death during study period. Urine albumin–creatinine ratio, alanineaminotransferase, aspartate aminotransferase and prothrombin time/International Normalized Ratio were found to be correlating with APACHE II scores and mortality significantly. Specific individual cut-offs were found for these parameters and were combined to form combined predictors which showed good discrimination (AUC = 0.715) and good calibration ($p = 0.811$) with specificity of 98.6% in predicting mortality. SIRS patients falling above combined predictor's cutoff are 54 times more likely to have an unfavorable outcome compared to the ones below. Overall predictive accuracy of first day combined predictors was such that within 24 h of ICU admission 87% of ICU SIRS admissions could be given a risk estimate for hospital death.

Keywords SIRS · Renal biomarker · Hepatic biomarker · Mortality · Critically ill · Combined predictors

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Introduction

Systemic inflammatory response syndrome (SIRS) is a frequently encountered complication seen in patients admitted in intensive care units and remains as a common cause of mortality. Prevalence of SIRS is very high, affecting one-third of all in-hospital patients, and more than 50% of all ICU patients [1, 2]. Current diagnosis of sepsis is based primarily on the criteria of American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) conference held in 1991 [3].

Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scoring system is one of the well accepted scoring system for assessment of prognosis among

critically ill patients admitted in ICU [4]. However they use multiple parameters which make it cumbersome for usage in day to day practice. Since sepsis induced hepatic and renal dysfunction is a frequent event and is strongly associated with mortality, this study is designed to look for relatively simple, easy to use hepatic and renal markers on par with APACHE II scoring system for prognostication of critically ill SIRS patients.

Materials and Methods

The study was conducted for a period of 1 year from Jan 2013 to Dec 2013 at a tertiary care hospital in south India after getting approval from the Institutional Scientific and Ethical committee. The patients admitted in ICU with SIRS, of age more than 18 years, were included in our study based on ACCP/SCCM guidelines (Supplementary Table 1) [3].

Patients were excluded if they had confounding factors such as anuria/oliguria, macroscopic hematuria, renal or postrenal cause of proteinuria like urinary tract infection previously documented chronic kidney disease, chronic liver disease, patients on anticoagulant medications, menstruating/ pregnant females and patients with drug overdose.

Selected patients were followed up for 28 days from the date of admission in order to categorize them as survivors (discharged within 4 weeks) or non-survivors (who succumbed to death within that time). Since we were looking only for in-hospital mortality rates, patients who died after discharge from the hospital were not considered as non-survivors. We identified 100 patients clinically confirmed with SIRS with ICU stay more than 24 h, out of which 87 patients fulfilled our inclusion criteria. Complete blood count, electrolytes, arterial blood gases were collected from the selected patients soon after admission in ICU. Spot urine microalbumin, urine creatinine, renal and liver function Tests, prothrombin time were evaluated at 24 h of admission for the same patients. Arterial blood gases were evaluated using Gem Premier 3000 ABG analyser, Electrolytes were measured using IL llyte electrolyte analyser, Prothrombin time was measured using CL analyser from Technomed with pre-programmed tests of PT Recombiplastin (with Recombiplastin having an ISI of 1.01 using which INR was evaluated from the instrument). All biochemical, urine investigations were carried out in Chemwell auto-analyser from CPC diagnostics. Complete hemogram was measured using UniCel DxH 800 analyzer with a 5-part differential. APACHE II scores were calculated manually and using web based calculators at 24 h of admission [5, 6].

Statistical Analysis

Data was analyzed using SPSS software 16.0 version for windows. The results were presented as median and 25th/75th percentiles (InterQuartile Range, IQR) (All data were found to be non-parametric). To compare two independent samples, we used Mann-Whitney *U*-test (All data were found to be non-parametric). Chi-Square test was used to compare proportions. The nonparametric Spearman ranked sign procedure was used to assess the significance of associations. A p value less than 0.05 was considered statistically significant. Receiver Operating Characteristic (ROC) curve was constructed to check for diagnostic accuracy of individual or combined variables to predict mortality. A binary logistic regression analysis was carried out to assess the effects of known and unknown confounders on each of the variables and combined predictors altogether.

Results

Out of 100 clinically confirmed SIRS patients with ICU stay more than 24 h, 87 patients were included in (Distribution of cases and the patients excluded are summarized in Supplementary Table 2). Out of 87 patients 49 (56%) were classified as sepsis patients (21 sepsis, 18 severe sepsis, 10 septic shock patients) and 34 (39%) patients as patients with non infectious SIRS condition. Four (5%) patients had multiple organ dysfunction syndrome. Thirty-nine percent of patients had pre-existing diabetes mellitus and 30% of patients had hypertension as per patient's records. Eighteen (21%) of the 87 patients had succumbed to death in ICU.

Supplementary Table 3 summarizes the baseline characteristics of all the patients included in our study. Median age of included patients was 65 years with 63% of male patients and remaining 37% females. Among the non survivors 55% were male and 45% were female. Of the total 39% of patients had preexisting diabetes mellitus, 30% had preadmission hypertension. Forty-one percent were smokers and 38% were found to be chronic alcoholics. Comparison between survivors and non survivors showed that the patients who died in ICU had significantly lower levels of ICU stay. Median age was higher among survivors (65 years) compared to non survivors (63 years) without any significant difference between them.

Comparison between survivors and non survivors summarized in Table 1 showed that the patients who died in ICU had a significantly higher median APACHE II score, ALT, AST, INR and urine ACR, However they had significantly lower levels of serum albumin. Serum urea,

Table 1 Comparison of APACHE II score, hepatic, renal and urine markers between survivors and non-survivors

	Survivors	Non-survivors	*p*-value
APACHE II score	17 (14–22)	27 (24–32)	< 0.001*
ALT (IU/L)	24 (19–43.5)	61.5 (35.8–259.8)	0.001*
AST (IU/L)	34 (25.5–62.5)	98 (35–348.8)	< 0.001*
Total bilirubin (mg/dL)	0.80 (0.70–0.90)	0.80 (0.80–0.90)	0.065
Direct bilirubin (mg/dL)	0.20 (0.20–0.30)	0.20 (0.20–0.30)	0.191
Total protein (g/dL)	6.9 (6.1–7.2)	6.3 (5.9–6.9)	0.178
Albumin (g/dL)	3.6 (3–4)	2.4 (2.8–3.4)	0.008*
International Normalized Ratio	1.0 (1.0–1.2)	1.3 (1.1–1.3)	0.002*
Urea (mg/dL)	35 (26–48)	39 (27–48.8)	0.473
Creatinine (mg/dL)	0.9 (0.8–1.2)	1.2 (0.9–1.6)	0.191
Urine albumin–creatinine ratio (mg/g)	70 (26.8–139.4)	226.3 (129–332.5)	< 0.001*

All values are expressed as Median and Inter Quartile Range (IQR) at 25th and 75th percentiles Comparison between survivors and non-survivors done by Mann Whitney test, *$p < 0.05$ was considered statistically significant

creatinine, total/direct bilirubin and total protein did not show any significant differences between two groups.

Correlation analysis was done for these parameters with mortality and APACHE II scoring (Table 2). For all patients, APACHE II score along with ALT, AST, INR and urine ACR, were found to have a strong positive correlation with mortality. Serum albumin alone has shown a significant negative correlation with mortality. Correlation of all these parameters with APACHE II has revealed a significant positive association for ALT, AST, INR, creatinine and urine ACR. We selected only the parameters which showed good correlation to both mortality and APACHE II scores for further analysis.

Supplementary Figure 1 shows the ROC curve for the selected parameters to check their efficacy in predicting mortality. The area under the ROC curve for mortality was highest for APACHE II (area under the curve 0.875) followed by AST (0.789), urine ACR (0.771), ALT (0.753) and INR (0.728). Cutoff values for the ROC curves of these parameters with their corresponding sensitivity and specificity are summarized in Table 3.

Table 2 Correlation of ALT, AST, INR, serum protein, albumin and urine ACR with mortality and APACHE II

Parameters	Mortality		APACHE II	
	*rs**	*p* Value	*rs**	*p* Value
APACHE II	0.527	< 0.001**	–	–
ACR	0.380	< 0.001**	0.348	0.001**
ALT	0.355	0.001**	0.258	0.016**
AST	0.406	< 0.001**	0.334	0.002**
INR	0.336	0.001**	0.355	0.001**
Serum total protein	− 0.145	0.179	− 0.166	0.125
Serum albumin	− 0.285	0.007**	− 0.208	0.053
Serum creatinine	0.141	0.192	0.396	< 0.001**

*Ranked Spearman's correlation **$p < 0.05$ was considered statistically significant APACHE II—Acute Physiology and Chronic Health Evaluation; ACR—urine albumin–creatinine ratio; ALT—alanineaminotransferase; AST—aspartateaminotransferase; INR—International Normalized Ratio

Using the cut off values obtained from Table 3, a second ROC curve was constructed for mortality by combining ALT, AST, INR, urine ACR and it was compared with APACHE II curve. The combined predictors showed an area under the curve of 0.715 as against 0.875 of APACHE II (Table 4, Supplementary Figure 2). To estimate diagnostic accuracy of the combined predictors in prediction of ICU mortality of SIRS/Sepsis patients, the sensitivity and specificity were determined and were compared with an illustrious APACHE II score of 25 (which roughly corresponds to 50% mortality). The combined predictors had a high specificity of 98.6% with a positive and negative likelihood ratio of 30.7 and 0.6 respectively in predicting mortality (Table 4, Supplementary Figure 2).

Table 5 summarizes the risk of an unfavorable outcome for combined predictors corrected for possible confounders. High odds ratio explains that the combined predictors are independent predictors of mortality. They do not seem to get affected by the age, sex, diabetic and hypertensive status, smoking and alcohol intake of the patients although the risk of mortality increased from 54.4 to 96.84 times after correcting for all these variables. Overall predictive accuracy of first day combined predictor was such that, within 24 h of ICU admission, 87.4% of ICU admissions could be given a risk estimate for hospital death (Pseudo $R^2 = 0.359$). This predictive accuracy increased to 88.5% (Pseudo $R^2 = 0.410$) after correcting for age, sex, diabetic/hypertensive status, smoking and alcohol intake. Hosmer and Lemeshow test of goodness of fit for combined

Table 3 AUC of ROC curve and cut off values of APACHE II, ALT, AST, INR and urine ACR with their corresponding to their maximum sensitivity and specificity

Parameters	AUC	95% CI	Cut off values	Sensitivity (%)	Specificity (%)
Apache II	0.875	0.799–0.951	> 25	66.7	88.4
ACR (mg/g)	0.771	0.650–0.891	> 140	77.8	76.8
ALT (IU/L)	0.753	0.613–0.892	> 36	77.8	71.0
AST (IU/L)	0.789	0.674–0.904	> 73	66.7	85.5
INR	0.728	0.575–0.882	> 1.1	72.2	73.9

APACHE II—Acute Physiology and Chronic Health Evaluation; ACR—urine albumin–creatinine ratio; ALT—alanineaminotransferase; AST—aspartateaminotransferase; INR—International Normalized Ratio; AUC—area under ROC curve

Table 4 Diagnostic accuracy of the combined predictors compared with that of APACHE II score in predicting mortality of SIRS/Sepsis patients admitted in ICU

	APACHE II (≥ 25)	Combined predictors (ALT > 36, AST > 73, INR > 1.1 and urine ACR > 140)
AUC of ROC	0.875	0.715
95% CI	0.799–0.951	0.558–0.872
Sensitivity (%)	66.7	44.4
Specificity (%)	88.4	98.6
PPV (%)	60.0	88.9
NPV (%)	91.0	87.2
LR^+	5.8	30.7
LR^-	0.4	0.6

APACHE II—Acute Physiology and Chronic Health Evaluation; AUC—area under ROC curve; PPV—positive predictive value; NPV—negative predictive value; LR^+—positive likelihood ratio; LR^-—negative likelihood ratio

Table 5 Binary logistic regression analysis of combined predictors for mortality

	Mortality OR (95% CI)	*p*-value
Patients values above combined predictors	54.40* (6.14–482.33)	< 0.001‡
Age	1.01 (0.96–1.06)	0.696
Males	1.52 (0.29–8.04)	0.621
Diabetics	1.09 (0.25–4.74)	0.911
Hypertensives	0.83 (0.15–4.46)	0.827
Smokers	0.06 (0.00–1.35)	0.076
Alcoholics	7.86 (0.36–144.20)	0.192
Patients values above combined predictors	96.84** (7.40–1266.82)	< 0.001‡

The dependent variables in the analysis is the mortality status

*Crude odds ratio [X^2—22.687 ($p < 0.001$), Pseudo R^2—0.359, 87.4% of cases correctly classified]

**Adjusted odds ratio after correcting for age, sex, diabetes, hypertension, smoking and alcohol intake [X^2—26.409 ($p < 0.001$), Pseudo R^2—0.410, 88.5% of cases correctly classified]

‡$p < 0.05$ was considered statistically significant Hosmer and Lemeshow Test for Goodness of Fit: X^2—4.482 (p 0.811) OR—Odds Ratio CI—Confidence Interval

predictors showed a Chi-square value of 4.482 with p value 0.811.

A second logistic regression analysis was performed to ascertain the effects on combined predictors by various critical analysis which are usually carried out for SIRS patients admitted in an ICU (Table 6). Results showed that increase in serum urea, sodium, bilirubin, white blood cell count and pCO_2 having a positive influence on the likelihood of patient entering above the cut-off for combined predictors whereas number of ICU days stay, mean arterial pressure, mean heart rate, serum creatinine, haemoglobin, potassium, bicarbonate, total protein and albumin having a negative influence for the same. The model could explain 65.5% of variance in combined predictors and correctly

Table 6 Logistic regression—impact of possible confounders on combined predictors

Confounders	Estimate	Mortality OR (95% CI)	*p*-value
Number of ICU stay (days)	− 1.029	0.357 (0.107–1.193)	0.094
Mean arterial pressure	− 0.097	0.908 (0.814–1.012)	0.082
Heart rate	− 0.099	0.906 (0.782–1.050)	0.188
Serum urea	0.157	1.169 (0.956–1.430)	0.128
Serum creatinine	− 5.736	0.003 (0.000–41.548)	0.235
WBC count	0.002	1.002 (0.881–1.139)	0.982
Hemoglobin	− 0.092	0.912 (0.403–2.066)	0.825
Serum sodium	0.051	1.052 (0.841–1.316)	0.657
Serum potassium	− 1.334	0.264 (0.020–3.490)	0.312
pCO_2	0.053	1.054 (0.978–1.137)	0.170
Bicarbonate	− 0.101	0.904 (0.684–1.193)	0.475
Bilirubin	0.447	1.564 (0.101–24.327)	0.749
Total Protein	− 1.060	0.346 (0.028–4.275)	0.408
Albumin	− 7.845	0.000 (0.000–6.745)	0.115

The dependent variable in the analysis are the patients falling above and below the cut-off of combined predictors [X^2—33.333 ($p = 0.003$), Pseudo R^2—0.655, 92% of cases correctly classified]

p-value < 0.05 considered statistically significant

classified 92% of them. However, none of these confounders were found to be influencing combined predictors significantly at 5% level.

Discussion

Systemic inflammatory response syndrome, as the name suggests provokes a systemic host response involving hundreds of mediators that could be potentially used as biomarkers for both for diagnosis and prognosis [7]. However, the main aim of this study was to look for relatively simple, easy to use biochemical markers, on par with APACHE II scoring system for prognostication of critically ill systemic inflammatory response syndrome (SIRS) patients. Of all the organs, liver and kidney both play a pivotal role in regulation of key metabolic, homeostatic and host-defense activities. Injury to these organs is considered one of the main factors for the development and progression of multiple organ failure which more often leads to death. Our results have shown that serum values of alanine and aspartate transaminases (ALT and AST), urine albumin creatinine ratio (ACR) and prothrombin time-International Normalized Ratio (PT-INR) were significantly elevated among non survivors. We measured all these parameters after 24 h of patients ICU admission in order to assess the efficacy of therapy on those selected patients. In sepsis literature the assessment of prognosis after 24 h of admission in ICU is often referred to as 'silver day [8]. Even APACHE II scoring is also done at that period.

Liver in critically ill conditions have two opposing roles. It acts as a source of inflammatory mediators and also as a target organ for the effects of inflammatory mediators [9]. Hepatic injury has been proved as independent contributor of mortality rates which also determines length of ICU stay [10]. Brun-Buisson et al. [11] in their EPISEPSIS study in French intensive care units had found that the persistence or development of liver failure in the 72-h period after onset of severe sepsis was strongly associated with mortality outcome. Similarly Marshall and colleagues while developing multiple organ dysfunction score evaluated the association of serum bilirubin, albumin, alkaline phosphatase, aspartate/ alanine aminotransferases and lactate dehydrogenase—with ICU mortality rate in 692 patients to find the ideal descriptor of liver dysfunction. Interestingly neither of them individually or in combination was able to predict mortality outcome in those patients. Since only bilirubin satisfied most of the criteria for the ideal descriptor of liver dysfunction the authors described bilirubin as hepatic component in their scoring [12]. However, they have also mentioned its lack of specificity and its inability to reflect full spectrum liver dysfunction. It also had a problem of differentiating an acute response from a pre-existing chronic organ disease [12]. Of note, neither APACHE II scores nor mortality had a significant association to total and direct bilirubin in our study. This is probably due to the exclusion of severe hepatic dysfunction patients in our study.

Primary or secondary hepatic injury can arise in a critically ill patient as a result of reduced perfusion to the liver (caused by low output septic shock) or as a late onset form of hepatic injury (secondary to hepatotoxic action of inflammatory mediators) [13]. The former is characterized by strikingly high levels of hepatic enzymes elevation.

However, a comparatively lower level of increase in hepatic enzymes especially transaminases has been documented due to secondary hepatic injury by inflammation [14]. Our findings have shown that transaminases were showing significant correlation to both APACHE II scores and mortality outcome of the patient. Other hepatic function marker like serum total protein was found to have no significant correlation to both APACHE II scores and mortality outcome in our study although serum albumin showed a significant negative correlation with only mortality. Our aim was to find an outcome predictor which correlates closely with both APACHE II scores and mortality. Hence we selected only transaminases as hepatic component for further analysis.

It has to be noted that transaminases in our study, at specific cut-offs can be used as an independent predictor of mortality among SIRS patients. Among those transaminases, AST seems to have a more significant positive association to both APACHE II scores and outcome of the patient compared to ALT. Hence cutoff value for mortality has been fixed a little higher for AST (73 IU/L) so as to increase the specificity of predicting mortality outcome. Interestingly, the sensitivity and specificity in outcome prediction was maximum for an ALT cut-off of 36 IU/L even though it was well within normal limits.

Likewise, among the renal parameters, only ACR seems to have a high degree of positive correlation to APACHE II scores as well as patient's mortality outcome. Reason is due to systemic capillary inflammation by inflammatory mediators among SIRS patients, like C-reactive protein (CRP), Tumor Necrotic Factor (TNFα), soluble intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin [15]. These lead to an increase in glomerular permeability to albumin and a reduction in tubular reabsorption [16, 17]. Also, the degree of microalbuminuria is dependent on degree of inflammatory response hence microalbuminuria reflects disease severity. This probably explains its positive association with APACHE II scores both of which quantify physiological response to acute inflammation and mortality outcome. We have left serum creatinine out because it will begin to rise only after the glomerular filtration rate falls to 60% of baseline [18, 19]. Studies indicate serum creatinine levels measured each day bear little real time correlation with renal function in critically ill patients [20]. Moreover our study showed significant correlation of serum creatinine only with APACHE II scores and not with mortality.

ACR indeed was found to be an independent predictor of mortality in a critical care setup. Forty-five percent of the patients in our study had urine ACR values more than our cut-off of 140 mg/g. Thorevska et al. in their study showed the association of urine albumin creatinine ratio (ACR) and clinical outcomes in 104 mixed ICU patients. They found that urine ACR $>$ 100 mg/g was an independent predictor of mortality and hospital stay [21]. Similar study done on 431 critical care patients by Gosling et al has concluded that urine albumin changes rapidly within the first 6 h following ICU admission and predicts ICU mortality and inotrope requirements better than APACHE II and SOFA scores [22].

Coagulopathy among SIRS patients may develop primarily due to sepsis or to treatments such as fresh frozen plasma. This actually contributes to adverse outcome by the development of transfusion associated acute lung injury [23] and transfusion associated circulatory overload [24, 25] during critical illness. It is characterized by PT prolongation which also happens to be a far more sensitive index of liver synthetic function than albumin and is strongly associated with greater risk of death in ICU [26]. The cutoff for abnormal international normalized ratio for clinical transfusion decision is to have INR value of more than 1.5. However we wanted to have a cutoff value of INR which shows a good sensitivity and specificity values for only mortality outcome. Hence for our analysis, we defined PT prolongation as INR of $>$ 1.1.

Values of ALT $>$ 36 IU/L, AST $>$ 73 IU/L, PT-INR $>$ 1.1 and urine ACR $>$ 140 mg/g were indeed good predictors of mortality individually and were correlating well with APACHE II scores. Although good statistically, some of those values are well within normal range therefore limiting its use as independent mortality predictor. In order to increase their prediction specificity, all these parameters were combined to form combined predictors. SIRS patients above combined predictor's cutoff (at 24 h of admission) are 54 times more likely to have an unfavorable outcome compared to the patients below the cut-offs in our study. The specificity of predicting mortality using combined predictor was 98.6% with a good discrimination (area under receiver operating characteristic curve $= 0.715$) and good calibration ($p = 0.811$). The overall accuracy of the model was 88.5% after correcting for confounders. It also correlates closely with the APACHE II scores and does not seem to get affected by the presence of various potential confounders.

Limitations of our study include all limitations of retrospective observational studies. Secondly, our study is just a single center study. Thirdly, the combined predictors developed here cannot be adapted universally to all the critically ill patients. This we feel is due to the exclusion of critically ill patients with clinically evident confounding factors such as chronic kidney disease, severe pre-existing hepatic abnormality (which can interfere with the transaminases value) and patients who had the risk for development of abnormal coagulation states. Lastly, the patients we took up were all from medical ICU and hence our results can't be generalized for surgical ICU patients.

Conclusion

The combined predictors of renal and hepatic markers although not a replacement of existing APACHE II scoring can be used to determine outcome of patients which will help in efficient planning and resource utilization and ultimately for a better patient triage and management.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Research Involving Human Participants Ethical Approval for this study has been obtained and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and research committee and with the 1964 Helsinki declaration and its later amendments.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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