

Predictors of mortality of severe sepsis among adult patients in the medical Intensive Care Unit

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ABSTRACT

Background: Sepsis is an important cause of mortality in the Intensive Care Units (ICUs) worldwide. Information regarding early predictive factors for mortality and morbidity is limited. **Aims and Objectives:** The primary objective of the study was to estimate the mortality of severe sepsis among adult patients admitted into the medical ICU. The secondary objective was to identify the predictors associated with mortality. **Materials and Methods:** Adult patients admitted with severe sepsis in the medical ICU were studied. The primary outcome was the mortality among the study population. Baseline demographic, clinical, and laboratory data were recorded upon inclusion into the study. Risk factors associated with mortality were studied by univariate analysis. The variables having statistical significance were further included in multivariate analysis to identify the independent predictors of mortality. **Results:** Out of eighty patients, 54 (67.5%) died. Univariate analysis showed that age >60 years, tachycardia, hypotension, elevated C-reactive protein (CRP) and lactate, thrombocytopenia, need of mechanical ventilation, and high Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment scores were variables associated with high mortality. The independent predictors of mortality identified by multivariate regression analysis were platelet count below 1 lakhs, serum levels of CRP >100, APACHE II score >25 on the day of admission to the ICU with severe sepsis, and the need for invasive mechanical ventilation. **Conclusions:** Low platelet count, elevated serum levels of CRP, APACHE score >25, and the need for invasive mechanical ventilation were found to be independent predictors of mortality of severe sepsis among adult patients with severe sepsis in the medical ICU.

KEY WORDS: Intensive Care Unit, mortality, predictors, severe sepsis

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INTRODUCTION

Sepsis is currently one of the important problems in medicine due to its complexity from pathophysiologic, clinical, and therapeutic viewpoints. Sepsis is an important cause of hospitalization and a major cause of death in the Intensive Care Units (ICUs) worldwide.^[1,2] The systemic, deleterious host response to infection is defined as sepsis. If not treated early, it can progress to severe sepsis and

lead to tissue hypoperfusion and hypotension called septic shock.^[3,4] Although sepsis is one of the leading causes of mortality in hospitalized patients, information regarding early predictive factors for mortality and morbidity is limited. This study was aimed to estimate the mortality of severe sepsis in adult patients admitted into the medical ICU and to identify the prognostic factors associated with the outcome of severe sepsis which were the predictors of mortality.

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MATERIALS AND METHODS

This was a prospective observational study conducted in the medical ICUs of tertiary care hospital located in Southern India, during January 2013–December 2014. Patients over 18-year-old admitted into medical ICUs meeting the criteria for severe sepsis and those patients admitted to the ICU who develop severe sepsis were included in the study. Institutional Ethics Committee clearance was obtained. Informed written consent was obtained from the patients' relatives.

Sepsis was defined as systemic inflammatory response syndrome (SIRS) with suspected or proven microbial etiology. SIRS includes the presence of at least two of the following: (1) body temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, (2) heart rate $>90/\text{min}$, (3) respiratory rate >20 breaths/min or hyperventilation with a $\text{PaCO}_2 <32$ mmHg, (4) white blood cell count $>12,000/\text{mm}^3$ or $<4000/\text{mm}^3$, or with $>10\%$ immature neutrophils.

Severe sepsis was defined as sepsis associated with organ dysfunction. Patients with SIRS but no probable or definite focus of infection, i.e., conditions that mimic sepsis by satisfying the criteria for SIRS, but with noninfectious causes were excluded from the study.

Baseline demographic, clinical, and laboratory data were recorded upon inclusion into the study. Clinical variables studied were age, sex, and location of patient, body temperature, resting heart rate, respiratory rate and mean arterial pressure, suspected source of infection, comorbid conditions, antibiotic regimen, requirement for invasive mechanical ventilation, and outcome. All the patients were subjected to chest X-ray, complete blood count, C-reactive protein (CRP), hepatic and renal function tests, serum electrolytes, arterial blood gases and prothrombin time. Blood cultures and cultures of specimens from the primary site of infection were done. Severity of sepsis was scored within 24 h of diagnosis of severe sepsis using the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scoring systems. Interventions including antimicrobial therapy were decided by the treating physicians. All patients were followed up until death or discharge from the ICU. Hospitalization outcome was defined as mortality or discharged improved.

Statistical analysis

Based on the mortality rate observed in severe sepsis from the existing literature (Boechat Tde *et al.*, 2012;^[5] Oppert *et al.*, 2008^[6]), and assuming the mortality in our study would be toward higher side and with 95% confidence and 20% allowable error, minimum sample size came to eighty. Percentage of mortality in severe sepsis among adult cases in the medical ICUs was computed. To test the statistical significance of the association between risk factors and mortality, Chi-square test was done. To test the statistical significance of the difference in the mean values

of measurable variables with respect to mortality, Student's *t*-test was done. Multivariate analysis was done by logistic regression method. $P < 0.05$ was taken as statistically significant. Receiver operating characteristic (ROC) curves were plotted for APACHE II and SOFA scores to identify the cut off.

RESULTS

There were eighty patients admitted to the ICU with a diagnosis of severe sepsis during study period and were included in the study. Of these, 57 were male (71.25%) and 23 (28.75%) were female. Maximum patients ($n = 65$) belonged to the age group of 50–80 years of age. Mean age of the study population was 60.97 years. Type 2 diabetes mellitus and systemic hypertension were the major comorbidities present in the study population, both being present in 37 patients each (46.25%). Respiratory comorbidities, chronic liver, and kidney diseases along with heart diseases were also present in a significant number of patients. Fever was the most common presenting feature (72.50%) followed by breathlessness (43.75%), cough (32.50%), abdominal, and neurologic symptoms. Based on the presenting symptoms and clinical examination findings, majority of the patients (66.25%) had respiratory tract as the suspected source of sepsis.

Of the total eighty patients, 63.75% of patients had had at least one organism isolated from either respiratory secretions, blood, urine, or other body fluids. Some had organisms isolated from different sources while some had multiple organisms isolated. Overall, the most common organisms isolated were *Klebsiella* species (24%) and *Acinetobacter baumannii* (23%). Blood cultures were positive in 27.5% cases which included *Staphylococcus aureus*, *Pseudomonas/Burkholderia* spp., *Klebsiella* spp., *A. baumannii*, and *Escherichia coli*. Majority of the organisms were isolated from respiratory secretions (41.25%) either from the sputum or a minibronchoalveolar lavage (BAL) specimen.

Out of eighty patients, 54 (67.5%) patients died [Figure 1]. The association between the primary outcome (mortality) and risk factors was assessed using the Chi-square test [Table 1]. Age >60 years was found to be a significant risk factor for mortality. The mortality was 79.5% (35) among the patients aged over 60 years who succumbed to severe sepsis (mortality group), whereas it was 52.5% (19) among the patients aged <60 years who survived ($P = 0.011$). Male gender was found to have greater mortality (73.7%) compared with female gender (52.2%), an observation was of borderline statistical significance.

Mortality rates were almost similar in those who had comorbidities such as diabetes mellitus, chronic liver and kidney diseases, and respiratory comorbidities as compared with those who had not and these were not found to be related to mortality in this study. The

mortality rates in those with respiratory source of sepsis were higher (71.7%) compared with those who had other focus of infection (59.3%) but was not statistically significant. Fifty-six (70%) patients with severe sepsis

Table 1: Association between risk factors and mortality (Chi-square test)

Risk factors	Classification (n)	Mortality, n (%)	P
Age	<60 (36)	19 (52.8)	0.011
	>60 (44)	35 (79.5)	
Sex	Male (57)	42 (73.7)	0.063
	Female (23)	12 (52.2)	
History of fever	Absent (22)	20 (90.9)	0.007
	Present (58)	34 (58.6)	
Diabetes mellitus	Absent (43)	30 (69.8)	0.641
	Present (37)	24 (64.9)	
Respiratory comorbidities	Absent (56)	38 (67.9)	0.917
	Present (24)	16 (66.7)	
CLD or CKD	Absent (56)	37 (66.10)	0.677
	Present (24)	17 (70.8)	
Source of sepsis	Respiratory (53)	38 (71.7)	0.261
	Other (27)	16 (59.3)	
Reduced urine output	Absent (21)	12 (57.1)	0.238
	Present (59)	42 (71.2)	
Invasive mechanical ventilation	Not done (24)	6 (25)	0.001
	Done (56)	48 (85.7)	
Culture results	Negative (29)	19 (65.5)	0.775
	Positive (51)	35 (68.6)	
Blood culture	Negative (58)	37 (63.8)	0.25
	Positive (22)	17 (77.3)	
Multiple isolates	Negative (52)	37 (71.2)	0.342
	Positive (28)	17 (60.7)	
<i>Acinetobacter/Klebsiella</i> isolates	Negative (47)	31 (66)	0.725
	Positive (33)	23 (69.7)	

CKD: Chronic kidney disease, CLD: Chronic liver disease

underwent invasive mechanical ventilation. The mortality rate among these patients was found to be significantly higher (85.7%) as compared with those who were treated without invasive mechanical ventilation (25.0%). Culture positivity, blood culture positivity, isolation of multiple organisms, and isolation of organisms such as *Klebsiella* species or *Acinetobacter* were not significantly related to mortality [Figure 2].

Comparison of difference of means by *t*-test was used to assess the significance of measurable variables with respect to the primary outcome, i.e., mortality [Table 2]. The mean age of those who succumbed to sepsis (63.19 ± 15.78) was higher than the survivors (56.35 ± 15.35), an observation of borderline significance. A higher heart rate at the time of diagnosis of sepsis was found to be related to mortality. A lower mean arterial pressure was observed in the mortality group with borderline significance. Hence, a higher heart rate and a lower mean arterial pressure could predict mortality in severe sepsis.

The mean platelet count in the survivor group was $240 \times 10^3/\text{mm}^3$ and in the mortality group, it was $97 \times 10^3/\text{mm}^3$ and this difference was statistically significant implying that a low platelet count in severe sepsis could be a predictor of mortality. Patients who succumbed to severe sepsis were having a higher mean CRP (184.55 ± 99.56) as compared with those who survived (66.59 ± 61.36) and higher serum lactate (4.42 ± 2.24 mmol/L) as compared with the survival group (2.28 ± 1.54 mmol/L). Hence, higher levels of CRP and lactate were associated with

Table 2: Association between risk factors and mortality (t-test)

Risk factors	Mean (SD)		P
	Survival (n=26)	Mortality (n=54)	
Age (years)	56.35 (15.35)	63.19 (15.78)	0.071
Temperature (°F)	99.73 (1.31)	99.53 (1.46)	0.538
HR (/min)	102.77 (21.66)	112.56 (19.91)	0.049
BP (MAP mmHg)	91.48 (14.81)	82.91 (20.55)	0.061
RR/mt	26.85 (5.69)	29.43 (7.53)	0.126
PaO ₂ /FiO ₂	238.25 (110.72)	220.80 (116.61)	0.526
WBC count/ml ³	17,575.38 (7475.95)	21,573.35 (29,817.71)	0.504
Neutrophil (%)	82.16 (11.03)	80.55 (19.00)	0.691
Platelet/ml ³	240,638.46 (105,967.59)	96,998.89 (66,335.57)	0.001
Hb (g/dl)	11.80 (1.96)	11.09 (2.79)	0.253
PCV (%)	35.09 (6.35)	32.97 (8.54)	0.264
CRP (g/dl)	66.59 (61.36)	184.55 (99.56)	0.001
Serum lactate (mmol/L)	2.78 (1.98)	4.42 (3.14)	0.006
Serum creatinine (mg/dL)	2.45 (1.54)	2.73 (2.24)	0.577
Serum sodium (mmol/L)	134.16 (7.05)	133.07 (9.85)	0.617
Serum potassium (mmol/L)	4.16 (0.79)	4.23 (0.89)	0.734
Serum bilirubin (mg/dL)	2.29 (2.11)	3.11 (4.07)	0.34
AST (IU/L)	441.31 (1004.92)	226.51 (470.01)	0.195
ALT (IU/L)	311.83 (605.44)	163.52 (430.76)	0.212
ALKP (IU/L)	227.57 (325.03)	153.78 (121.54)	0.144
Serum albumin (g/dL)	2.73 (0.54)	2.69 (0.52)	0.777
INR	1.52 (1.09)	1.77 (1.11)	0.351
APACHE II score	17.54 (4.50)	28.13 (6.25)	0.001
SOFA	7.54 (2.75)	11.94 (3.10)	0.001

APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, INR: International normalized ratio, ALT: Alanine transaminase, AST: Aspartate aminotransferase, ALKP: Alkaline phosphatase, CRP: C-reactive protein, HR: Heart rate, BP: Blood pressure, MAP: Mean arterial pressure, WBC: White blood cell, RR: Respiratory rate, Hb: Hemoglobin, PCV: Packed cell volume, SD: Standard deviation

higher mortality rates. Serum levels of creatinine or sodium and potassium were not found to have association with mortality. None of the difference in mean values of liver enzymes, serum bilirubin, serum albumin, and international normalized ratio between the mortality and survivor groups was statistically significant.

The mean APACHE II score among those who succumbed (28.13 ± 6.25) was found to be significantly higher than the mean score among those who survived (17.54 ± 4.50). The mean SOFA score at the time of admission to the ICU with severe sepsis was also higher in the mortality group (11.94 ± 3.10) on comparison with that in the survivor group (7.54 ± 2.75), which was statistically significant. ROC curves were constructed for APACHE II and SOFA scores to identify cut offs that can predict mortality with optimum sensitivity and specificity. The area under the ROC was 0.928. The cut off for APACHE II score identified was 21.5 with a sensitivity of 87% and specificity of 81% with an area under the ROC of 0.928. For SOFA score, the area under the ROC was 0.855. A cut off score of 8.5 was identified with a corresponding sensitivity and specificity of 87% and 65%, respectively [Figures 3 and 4].

Multivariate logistic regression analysis [Table 3] was done to identify the independent risk factors related to the primary outcome [Table 2]. Platelet count <1.0 lakhs/mm³ ($P = 0.026$), serum level of CRP > 100 ($P = 0.008$), APACHE II score more than 25 points ($P = 0.006$), and undergoing invasive mechanical ventilation ($P = 0.014$) were identified as significantly related to the primary outcome; making these the important predictors for mortality among patients admitted with severe sepsis in the medical ICU.

DISCUSSION

This study was aimed at estimating the mortality rate among adult patients admitted in the medical ICU with severe sepsis and to identify risk factors which are predictors of short-term mortality. The mortality rate was found to be 67.5% in this study. The mortality rate was significantly higher in the age group over 60 years, approximately 80%. Diabetes mellitus and chronic respiratory disorders were found to be not related to mortality, an observation similar to the Outcomerea study.^[7] Although the most common suspected source of infection in the present study was found to be respiratory tract (66.25%), it was not related to increased

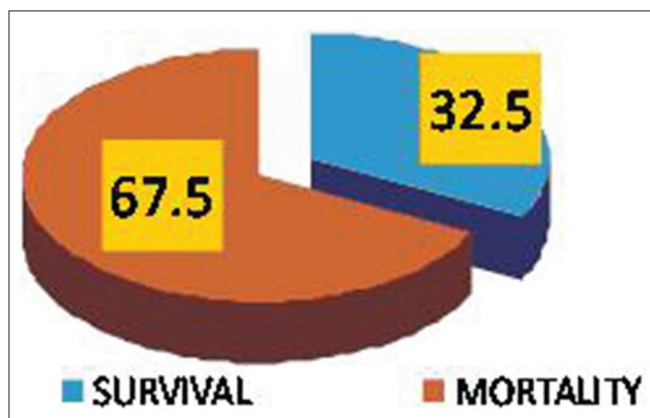


Figure 1: Pie chart showing mortality

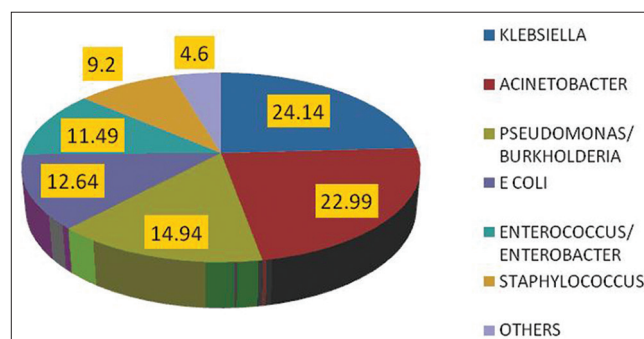


Figure 2: Pie chart showing organisms isolated

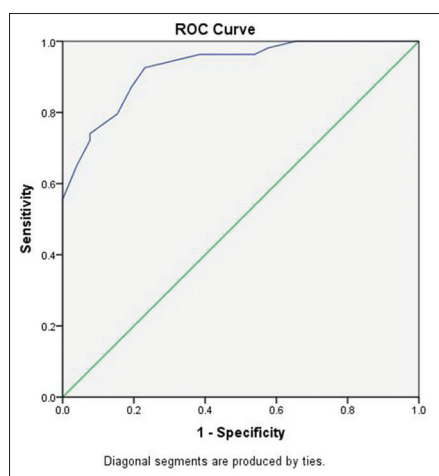


Figure 3: Receiver operating characteristic curve for Acute Physiology and Chronic Health Evaluation II score

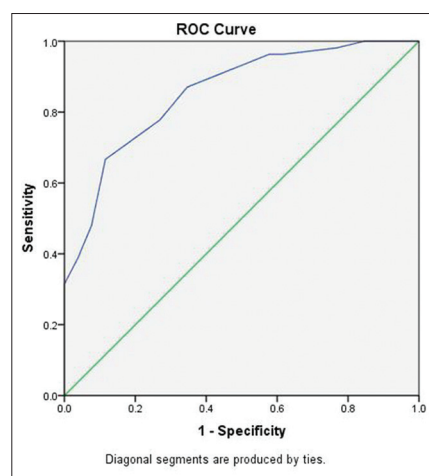


Figure 4: Receiver operating characteristic curve for Sequential Organ Failure Assessment score

mortality as observed in other studies.^[8-11] Infection could be documented in 63.75% of the study subjects, with at least one organism isolated in culture. A similar study by Zanon *et al.* had reported infectious SIRS of 71.3%.^[8] Majority of the organisms were isolated from respiratory secretions either from the sputum or mini-BAL specimens. Neither blood culture positivity nor isolation of multiple organisms was found to be significantly related to mortality. In the present study, the most common organisms were Gram-negative bacteria which were similar to the study by Zanon *et al.*^[8]

Mechanical ventilation was required in 56 (70%) of the eighty patients treated for severe sepsis as most of the patients had respiratory failure. Out of 56 ventilated patients, 48 (85.72%) patients succumbed despite the interventions. The mechanical ventilation was associated with higher mortality as seen in study by Vincent *et al.*^[10] This observation was statistically significant implying that undergoing invasive mechanical ventilation could be a predictor of mortality in severe sepsis. On multivariate logistic regression analysis, invasive mechanical ventilation in patients with severe sepsis was identified to be an independent predictor of mortality. A higher heart rate and lower mean arterial pressure at the time of admission to the ICU could be predictors of mortality of severely septic patients admitted to the ICU though these observations were of borderline statistical significance.

In this study, the mean platelet count was found to be lower among the patients who succumbed as compared with the survivors. Several other studies have also documented a low platelet count as a risk factor for mortality.^[12,13] Serum levels of CRP at the time of admission to the ICU with severe sepsis were identified as an independent predictor of mortality in this study. This observation was in concurrence with other studies.^[14,15] Serum levels of lactate have been identified as a predictor of mortality in

several studies^[16,17] and its importance is emphasized in the treatment of sepsis, where some treatment strategies depend on lactate levels.^[18] In our study also, higher serum lactate was found in the patients who died of severe sepsis. There was no significant difference in the mean values of serum creatinine among the survivors and nonsurvivors. This was in contrast to a study by Oppert *et al.* who had found acute renal failure a significant independent risk factor for mortality in patients with severe sepsis and septic shock.^[6]

APACHE II score on admission is a standard predictor of mortality in critically ill patients, including septic patients.^[19] In our study, the difference of mean APACHE II scores between the survivors and nonsurvivors was significant and was identified as an independent predictor of mortality in severe sepsis. There was a significant difference of the mean SOFA values among the nonsurvivors and survivors of severe sepsis, which were 11.94 and 7.54, respectively. Similar studies had identified SOFA scores in patients in the ICU at presentation and at 48 h, to be important parameters for predicting mortality.^[20] In the present study, a cut off for APACHE II score of 21.5 and SOFA 8.5 was associated with higher mortality with a sensitivity of 87% each and specificity of 81% and 65%, respectively. Zanon *et al.* in their Brazilian study had found APACHE II score cut off of 18 had sensitivity of 67.6% and specificity 66.6%.^[8] Hence, the scoring done on the day of admission, both APACHE II and SOFA should be used to identify patients with severe sepsis, who are at increased risk of short-term mortality, so that adequate interventions can be planned to modify the outcome.

The variables which were found to be statistically significant were compared with previously published Indian and international studies. The comparison is shown in Table 4.

Table 3: Multivariate regression analysis

Risk factor	P	OR	95% CI	
			Lower	Upper
Platelet count (<1×10 ³ µL)	0.026	28.08	1.505	523.81
CRP (>100 mg/L)	0.008	55.75	2.802	1108.870
APACHE II (score>25)	0.006	395.01	5.769	27,046.420
Need for invasive mech. ventilation	0.014	50.17	2.205	1141.612

CRP: C-reactive protein, APACHE: Acute Physiology and Chronic Health Evaluation, OR: Odds ratio, CI: Confidence interval

Table 4: Comparison with similar studies

Study	Sample size	Mortality rate (%)	Predictors
Boechat Tde <i>et al.</i> , Brazil, 2012 ^[5]	56	62.5	Thrombocytopenia
Oppert <i>et al.</i> , Germany, 2008 ^[6]	415	55.2	Acute renal failure
Sinkovic <i>et al.</i> , Slovenia, 2014 ^[21]	102	62.7	Serum lactate, APACHE II
Bale <i>et al.</i> , India, 2013 ^[22]	40	62.5	SOFA score
Shrestha <i>et al.</i> , India, 2012 ^[23]	100	55.7	Anemia, SOFA score, SAPS II, SAPS III scores
Mohan <i>et al.</i> ^[24]	100	53	SAPS II, SAPS III, anemia, SOFA score
Present study	80	67.5	CRP, platelet count, APACHE II score, mechanical ventilation

CRP: C-reactive protein, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, SAPS: Simplified Acute Physiology Score

CONCLUSIONS

The present study showed 67.5% mortality among the patients with severe sepsis. Low platelet count, high CRP, and elevated levels of serum lactate along with need for invasive mechanical ventilation were found to be a clear predictor of mortality in severely septic patients. APACHE II and SOFA score of more than 25 and 8.5, respectively, at the time of admission to the ICU with

severe sepsis were identified as independent predictors of mortality. Early identification of the predictors of mortality should enable us to do necessary interventions toward surviving the severe sepsis.

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Conflicts of interest

There are no conflicts of interest.

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