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Original Article

Internal Medicine Section

A Prospective Study of Comparison of APACHE-IV & SAPS-II Scoring Systems and Calculation of Standardised Mortality Rate in Severe Sepsis and Septic Shock Patients

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ABSTRACT

Context: Severe sepsis and septic shock are major causes of mortality in the Intensive Care Unit (ICU) Illness Scoring Systems can help in the prediction of outcome of these patients.

Aim: To calculate and compare APACHE-IV and SAPS-II Scoring Systems along with calculation of Standardised Mortality Rate (SMR) in patients of severe sepsis and septic shock in the ICU.

Study Design: Observational-analytical prospective study.

Materials and Methods: The study was conducted on 84 patients with severe sepsis and septic shock admitted to the Medical ICU of a tertiary care teaching hospital.

Results: Mean of Predicted Mortality Rate (PMR) for APACHE-IV was 37.85% and for SAPS-II, it was 72.36% which shows that APACHE-IV had under-predicted overall mortality while SAPS-II had over-predicted overall mortality of patients with severe sepsis and septic shock. Standardised Mortality Rate for APACHE-IV was 1.60 and for SAPS-II, it was 0.83.

Conclusion: Predicted Mortality of APACHE-IV and SAPS-II Scoring Systems did not correlate with the observed mortality for patients with severe sepsis and septic shock.

Keywords: APACHE-IV, SAPS-II, Septic shock, Severe sepsis, Standardised mortality rate

INTRODUCTION

Severe sepsis and septic shock are major reasons for Intensive Care Unit (ICU) admissions and the leading causes of mortality in non-coronary ICUs [1-3]. There is a lack of an agreed severity of illness scoring system for patients with sepsis. In the absence of such a system, it is difficult to interpret sepsis outcome studies [4]. Mortality Prediction Systems have been introduced as tools for assessing the performance of ICUs [5,6]. Prognostic scoring systems have a number of applications. They help in individual patient outcome prediction by reducing uncertainty and provide an opportunity for improved decision making. Prognostic scoring systems can facilitate quality assessment of an individual ICU by allowing comparison of its overall performance to a large scale representative database.

The 3 commonly used scoring systems are Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS) and Mortality Probability Model (MPM).

The present study attempts to use APACHE-IV and SAPS-II scoring systems to assess the Predictive Mortality in a Medical ICU in patients of severe sepsis and septic shock and to compare these values with the Actual Mortality Indices.

Aims and Objectives

1. To calculate APACHE-IV Scoring System in patients of severe sepsis and septic shock in the ICU.
2. To calculate SAPS-II Scoring System in patients of severe sepsis and septic shock in the ICU.
3. To compare both the scoring systems and to calculate Standardised Mortality Rate.

MATERIALS AND METHODS

This observational-analytical prospective study was carried out in the Medical ICU of a tertiary care teaching hospital from January 2008 to June 2009. The study included 84 patients admitted to the ICU with severe sepsis and septic shock.

Inclusion criteria

Patients admitted in Medical ICU meeting the diagnostic criteria for severe sepsis and septic shock during the first 24 h of admission.

1. Severe sepsis-Sepsis with one or more signs of organ dysfunction.

a) Cardio-vascular system-Systolic Blood Pressure (SBP) of less than or equal to 90 mm Hg that responds to administration of intravenous fluids.

b) Renal-Urine output less than 0.5 ml/kg/hour for one hour despite adequate fluid replacement.

c) Respiratory system-PaO_2/FiO_2 ratio below 250.

d) Metabolic-pH less than 7.3 or a base deficit of more than 5 mEq/L and a plasma lactate level more than 1.5 times of the upper limit of normal value.

e) Hematologic system-Platelet count below 80,000/mm^3.

2. Septic shock-Sepsis with hypotension (SBP less than 90 mm Hg) for at least one hour despite adequate fluid resuscitation (indicated by CVP value above 8 mm Hg) or the need for vasopressors to maintain SBP greater than 90 mm Hg.

Exclusion criteria

1. Patients whose duration of stay in ICU was less than 4 h.
2. Patients in vegetative state.

The patients were grouped according to the aetiology of their illness e.g. tropical infection, respiratory infection, genito-urinary infection etc. A thorough clinical examination was carried out in all patients. Total leucocyte count, Packed Cell Volume (PCV), serum creatinine, serum bilirubin, serum sodium/potassium/bicarbonate and arterial pH was done in each patient.

For calculating APACHE-IV score, following data was collected-

1. Acute Physiology Points-Both worst and best value in the first 24 h of admission to ICU was collected for a) Temperature b) Pulse c) Blood Pressure d) Respiratory Rate e) Haematocrit f) Total Leucocyte

Age (y)	Number of patients (n)	Percentage (%)
16-20	7	8.33
21-30	29	34.52
31-40	14	16.67
41-50	11	13.10
51-60	10	11.90
61-70	9	10.71
71-80	4	4.76

[Table/Fig-1]: Age composition of study subjects

Diagnosis	Number of patients (n)	Percentage (%)
Respiratory sepsis	29	34.51
1. Pneumonia	9	10.71
2. Tuberculosis	8	9.52
3. Chronic Obstructive Pulmonary Disease	4	4.76
4. Restrictive Lung Disease	3	3.57
5. Acute Respiratory Distress Syndrome	5	5.95
Tropical Infection	12	14.28
1. Malaria	10	11.90
2. Tetanus	2	2.38
Cardio-vascular disease	4	4.76
1. Congestive Cardiac Failure	3	3.57
2. Rheumatic Heart Disease	1	1.19
Obstetric sepsis	5	5.95
Surgical sepsis	2	2.38
CNS sepsis	13	15.47
1. Meningitis	9	10.71
2. Guillain-Barre Syndrome	4	4.76
GI sepsis-Gastroenteritis	4	4.76
Hepatic sepsis-Cirrhosis of liver	3	3.57
Uro-sepsis-Urinary Tract Infection	2	2.38
Cellulitis-Snake bite	3	3.57
Miscellaneous	7	8.33
1. Malignancy	4	4.76
2. Diabetic Keto-acidosis	3	3.57

[Table/Fig-2]: Diagnosis of study subjects on admission

Count g) Serum Blood Urea Nitrogen (BUN) h) Serum creatinine i) Serum sodium.

Single worst value in first 24 h was collected for a) FiO_2 b) PaO_2 c) PCO_2 d) pH e) Urine output f) Serum albumin g) Serum bilirubin h) Glasgow Coma Scale.

2. Age of the patient

3. Chronic Health Evaluation-Was done to know if the patient had severe organ system insufficiency or was immunocompromised. Conditions included are a) Chronic Liver Disease b) Leukemia/ Lymphoma c) Acquired Immune Deficiency Syndrome (AIDS) d) Cancer metastasis e) Chronic Renal Insufficiency.

4. ICU admission information-Whether patient was admitted to ICU directly from Emergency Room or was transferred from other ward or some other hospital to ICU was noted.

5. Pre-ICU length of stay-Number of days for which patient was admitted in ward before being transferred to ICU.

6. Emergency Surgery in ICU

7. Re admission to ICU

8. Requirement of ventilatory support

9. Thrombolytic therapy-If the patient was diagnosed to have Acute Myocardial Infarction.

10. Primary admission diagnosis.

Variable	Mean Score	Predicted Mortality Rate (PMR) %	Actual Mortality Rate (AMR) %	Standardised Mortality Rate (SMR) = AMR/ PMR
APACHE IV	97.42 ± 19.51	37.85	60.71	1.60
SAPS II	68.20 ± 19.63	72.36	60.71	0.83

[Table/Fig-3]: Mortality chart

Parameter		Survivors Mean ± SD	Non-survivors Mean ± SD	p-value	Significance
Mean Temperature (°F)	High	100.776 ± 2.08	101.97 ± 1.874	0.008	Highly Significant
	Low	99.121 ± 2.19	100.02 ± 1.749	0.041	Significant
Mean Systolic BP(mm Hg)	High	86.24 ± 7.98	85.29 ± 10.45	0.658	Not Significant
	Low	66.12 ± 19.42	55.56 ± 29.14	0.05	Significant
Mean Diastolic BP(mm Hg)	High	52.606 ± 20.62	43.05 ± 27.06	0.071	Not Significant
	Low	12.424 ± 22.64	13.72 ± 22.71	0.798	Not Significant
Mean Heart Rate(/ minute)	High	116.39 ± 9.32	121.57 ± 6.60	0.004	Highly Significant
	Low	105.00 ± 7.20	109.65 ± 6.37	0.003	Highly Significant
Mean Respiratory Rate(/ minute)	High	31.55 ± 5.77	32.82 ± 5.56	0.314	Not Significant
	Low	25.97 ± 4.97	27.12 ± 5.50	0.335	Not significant
Urine output(ml)		848.48 ± 1507.09	373.53 ± 309.57	0.032	Significant
Glasgow Coma Scale		8.576 ± 2.25	5.92 ± 3.05	0.001	Highly Significant

[Table/Fig-4]: Comparison of clinical profile of study subjects according to outcome

The data collected from patients was converted to APACHE-IV Score and Predicted Mortality Rate by readymade software programmed by Mazen Kherallah. (Site-http:/www/icumedicus.com/icu_scores/apache IV.php)

SAPS-II Scoring System was calculated using the following variables-

1. Acute Physiology Points-Both best and worst value in first 24 h of admission to ICU was collected for a) Pulse b) Temperature c) Systolic BP d) Total Leucocyte Count e) Serum BUN f) Serum sodium g) Serum potassium h) Serum bicarbonate.

Single worst value in first 24 h was collected for a) FiO_2 b) PaO_2 c) pH d) Urine output e) Serum bilirubin f) Serum albumin g) Glasgow Coma Scale.

2. Age of patient

3. Type of admission

4. Mechanical ventilation

5. Chronic Health Evaluation-Conditions included were a) Hematologic malignancy b) AIDS c) Cancer metastasis.

The data collected from patients was converted to SAPS-II Score and Predicted Mortality Rate by software programmed by Mazen Kherallah. (Site-http:/www/icumedicus.com/icu_scores/saps.php).

Comparison of both scoring systems was done in terms of Predicted and Actual Mortality Rates. The Standardised Mortality Rate was calculated by dividing Actual Mortality Rate by Predicted Mortality Rate for both the systems.

Data were expressed as mean, standard deviation and percentages. Unpaired student's t-test and chi-square test were used to analyse the data. Statistical software SPSS was used for statistical analysis. p-value less than or equal to 0.05 was considered to be statistically significant for all statistical comparisons.

Parameter		Survivors Mean ± SD	Non-survivors Mean ± SD	p-value	Significance
Sodium	High	126.64 ± 8.13	125.11 ± 10.31	0.477	Not Significant
	Low	119.15 ± 9.87	117.45 ± 10.45	0.459	Not Significant
Potassium	High	4.14 ± 0.67	4.28 ± 0.72	0.354	Not Significant
	Low	3.35 ± 0.52	3.51 ± 0.79	0.292	Not Significant
Glucose	High	154.03 ± 68.32	163.45 ± 64.31	0.524	Not Significant
	Low	128.03 ± 47.05	133.76 ± 49.20	0.597	Not Significant
Creatinine	High	2.94 ± 1.88	3.89 ± 2.75	0.084	Not Significant
	Low	2.20 ± 1.36	2.69 ± 2.22	0.256	Not Significant
Blood Urea Nitrogen	High	46.04 ± 29.05	55.32 ± 27.33	0.142	Not Significant
	Low	38.18 ± 25.45	44.29 ± 24.68	0.276	Not Significant
Hematocrit	High	29.69 ± 6.40	30.37 ± 6.86	0.654	Not Significant
	Low	25.97 ± 5.83	25.35 ± 6.41	0.655	Not Significant
WBC count	High	12906.06 ± 5533.25	20115.69 ± 23693.86	0.041	Significant
	Low	10096.97 ± 3806.28	16178.43 ± 20369.68	0.042	Significant
Bicarbonate	High	22.42 ± 5.02	18.80 ± 5.96	0.005	Highly Significant
	Low	18.63 ± 4.78	16.12 ± 5.64	0.037	Significant
FiO_2		28.18 ± 23.06	53.52 ± 39.26	0.001	Highly Significant
pH		7.31 ± 0.07	7.25 ± 0.08	0.001	Highly Significant
pO_2		76.92 ± 14.56	68.14 ± 27.53	0.061	Not Significant
pCO_2		37.86 ± 8.27	40.37 ± 11.67	0.251	Not Significant
Albumin		2.97 ± 0.61	2.57 ± 0.61	0.004	Highly Significant

[Table/Fig-5]: Comparison of laboratory profile of study subjects according to outcome

RESULTS

Eighty four patients fulfilling the inclusion criteria were recruited as study subjects.

This study showed that majority of subjects were in the age group of 21-50 y (64%). Mean age of the study subjects was 40.60 ± 17.24 yrs [Table/Fig-1].

Out of 84 study patients, 50 were males and 34 were females. Majority of study patients were admitted directly to ICU through the Emergency Room while others were transferred from other wards of the hospital to ICU or were referred to the ICU from other hospitals.

Majority of the study patients had Respiratory Sepsis that was followed by tropical infections [Table/Fig-2]. Out of 84 study patients, 12 had some chronic disease (chronic renal failure, cirrhosis of liver, AIDS, metastatic cancer, multiple myeloma).

The Actual Mortality Rate (AMR) in this study was 60.71% since 51 out of the 84 study patients had expired. Mean of Predicted Mortality Rate (PMR) for APACHE-IV was 37.85% and for SAPS-II, it was 72.36% which shows that APACHE-IV had under-predicted overall mortality while SAPS-II had over-predicted overall mortality. Standardised Mortality Rate (SMR) was calculated by dividing AMR by PMR [Table/Fig-3].

Organ involved	Total number of patients	Survivors	Non-survivors	p-value
Heart	81	32	49	0.05
Lung	66	21	45	0.003
Acidosis	56	17	39	0.003
Kidney	54	15	39	0.001
Liver	17	5	12	0.09

[Table/Fig-6]: Incidence of organ failure and association with mortality

Apache-IV Score	Actual Mortality (%)	Predicted Mortality (%)
61-70	25	7.45
71-80	26.66	20.64
81-90	50	27.06
91-100	66.66	31.58
101-110	73.33	46.45
111-120	100	57.75
121-130	100	68.04
131-140	33.33	72.14
141-150	100	76.62

[Table/Fig-7]: Comparison of APACHE-IV score and mortality rates

SAPS-II Score	Actual Mortality Rate (AMR) (%)	Predicted Mortality Rate (PMR) (%)
21-30	0	8.5
31-40	28.57	19.14
41-50	20	35.4
51-60	46.66	59.8
61-70	50	76.16
71-80	90.90	89.63
81-90	69.23	93.84
91-100	100	97.5
101-110	100	99
111-120	100	100

[Table/Fig-8]: Comparison of SAPS-II score and mortality rates

The highest and lowest readings of temperature and heart rate in the first 24 h of ICU stay were found to be higher in non-survivors as compared to the survivors. Likewise, the lowest value of SBP in the first 24 h along with urine output and Glasgow Coma Scale (GCS) rating was significantly low in non-survivors [Table/Fig-4].

Non-survivors had significantly high leucocyte count and FiO when compared with survivors; while survivors had significantly higher serum bicarbonate, albumin and pH as compared to non-survivors [Table/Fig-5].

Most common organ failure in the study patients was cardio-vascular failure followed by respiratory failure [Table/Fig-6].

As the total score of the APACHE-IV Scoring System increased, both PMR and AMR increased. AMR was higher than PMR of almost all APACHE-IV Scores [Table/Fig-7]. SAPS-II Score also had a direct relationship with AMR and PMR. However, for each score, PMR was higher than AMR for SAPS-II [Table/Fig-8].

DISCUSSION

Sepsis is an infection-induced syndrome characterized by a number of symptoms and clinical signs including fever or hypothermia, leucocytosis or leucopenia, tachycardia and tachypnea [7]. If organ-system failure is associated with the condition, sepsis is considered to be severe.

The mean score of APACHE-IV and SAPS-II of the subjects in this study was 97.42 ± 19.51 and 68.20 ± 19.63 respectively. Mean

Predicted Mortality Rate for APACHE-IV and SAPS-II were 37.85% and 72.36% respectively. But the Actual Mortality rate was 60.71%. Thus, APACHE-IV under-predicted mortality while SAPS-II over-predicted mortality of the study subjects, giving a Standardized Mortality Rate of 1.60 and 0.83 respectively.

The measures of the severity of illness (scores) are used as an important tool after admission to predict the outcome of patients. APACHE and SAPS scoring systems are commonly used in judging disease severity and organ failure in critically ill patients.

A multicentric, prospective observational study done in India, to determine the incidence and outcome of severe sepsis among adult patients found the median APACHE II score to be 22. The Standardised Mortality Ratio was found to be 1.40 in the study [8].

A European study was carried out in a single-center Intensive Care Unit (ICU) to validate the SAPS II and APACHE II scores. In this study, the observed hospital mortality of patients with risk of death higher than 60% was overpredicted by SAPS II and underpredicted by APACHE II. This study validated both SAPS II and APACHE II scores in the ICU population which comprised mainly of surgical patients [9].

A study done in a tertiary care hospital in Saudi Arabia showed that predicted mortality by SAPS II and APACHE II systems was not significantly different from the actual mortality. The Standardised Mortality Ratio for APACHE II was 1.00 and that of SAPS II was 1.09 in this study [10].

Another study was conducted in a tertiary care medical/surgical Intensive Care Unit in Saudi Arabia to assess the validity of mortality prediction systems in patients admitted to the ICU with severe sepsis and septic shock. APACHE II and SAPS II scores were included in the study. Predicted and actual mortality rates along with standardised mortality ratio were calculated. Calibration, as tested by C-statistics, was poor for both APACHE II and SAPS II scores. The study concluded that though general ICU mortality system models had accurate mortality prediction, they had poor calibration. However, customization of SAPS II improved calibration. The customized model may be a useful tool when evaluating outcomes in patients with sepsis [11].

As new and effective therapeutic agents are becoming available, it is important that epidemiologic data be updated in order to better understand the incidence and pathophysiology of the disease and to plan the rational treatment of patients.

The manifestations of response to sepsis are usually super-imposed on the symptoms and signs of the patient are underlying illness and primary infection. However, there are individual variations in the clinical presentation. Hyper-ventilation is an early sign of sepsis. Oliguria in sepsis occurs secondary to shock that causes diminished renal perfusion leading to Acute Renal Failure. Insulin resistance and hyperglycemia are invariably present in sepsis. Hyperglycemia needs to be corrected since high blood glucose levels increase the risk of infection, delays wound healing, impairs neutrophil function and stimulates blood coagulation [12]. Anaemia is common in sepsis and results from depression of erythropoiesis.Hematocrit values of less than 30% have been used as an indication of blood transfusion in patients with sepsis with good results.

The Institute for Healthcare Improvement (IHI) has highlighted sepsis as an area of focus and has identified several deficiencies that may cause sub-optimal care of patients with severe sepsis. These deficiencies include inconsistency in the early diagnosis of severe sepsis and septic shock, frequent inadequate volume resuscitation without defined endpoints, late or inadequate use of antibiotics, frequent failure to support the cardiac output when depressed, frequent failure to control hyperglycemia adequately, frequent failure to use low tidal volumes and pressures in Acute Lung Injury (ALI) and frequent failure to treat adrenal insufficiency in refractory shock. Although the mortality rate for severe sepsis is 30 to 50%, this increases to 80 to 90% for septic shock with multiple organ dysfunction [13].

The aims of clinical evaluation in cases of sepsis are-

1. Establishment of a diagnosis.
2. Estimation of severity and prognosis of the condition.
3. Identification of the underlying cause.

The measures of the severity of illness (Scores) are used as an important tool after admission to predict the outcome of the patient. Mortality risk stratification in severe sepsis and septic shock is commonly used in clinical trials and in practice, which helps to improve accuracy when evaluating new therapies [14]. By facilitating comparison of the actual with predicted mortalities, the use of such Scoring Systems can provide valuable information about the performance of individual ICUs in treating patients with sepsis.

Severity of illness Scoring Systems are relatively simple to use and widely available. But, there is no ideal system for patients with sepsis. Most of the systems were developed for ICU patients in general and when applied to a particular group of patients, such as those with sepsis, their accuracy declines.

The advantages of an internationally valid mortality prediction system for patients with severe sepsis and septic shock are-

1. It will be useful in comparing the outcomes of patients between different ICUs and countries.
2. It will allow grouping of patients for enrolment in clinical trials. This will be of particular value when conducting large, international multi-centre studies.

This study has used APACHE-IV and SAPS-II Scoring Systems for risk stratification as outcome prediction models and gives some insight into the issue of the outcome of septic patients from a tertiary care perspective. Customization of these systems to predict the outcome of sepsis is an attractive option.

LIMITATIONS

1. Sample size was small and people from higher socio-economic status could not be included in the study.
2. Patients could not be subjected to thorough investigations because of financial constraints.

CONCLUSION

The present study shows that neither APACHE-IV nor SAPS-II Scoring System performed well in predicting mortality in patients with severe sepsis and septic shock. However, Discrimination (ability to distinguish between survivors and non-survivors) of SAPS-II was better than that of APACHE-IV for patients with severe sepsis and septic shock.

REFERENCES

[1] Rangel-Frausto MS. The epidemiology of bacterial sepsis. *Infect Dis Clin North Am.* 1999;13:299-312.
[2] Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome and associated costs of care. *Crit Care Med.* 2001;29:1303-10.
[3] Angus DC, Wax RS. Epidemiology of sepsis: an update. *Crit Care Med*. 2001;29 (Suppl 7):S109-16.
[4] Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time? *Crit Care Med.* 1998;26:2078-86.
[5] Lemeshow S, Le Gall Jr. Modelling the severity of illness of ICU patients. *JAMA* 1994;272:1049-55.
[6] Lemeshow S, Teres D, Klar J, Avrunin JS, Gehlbach SH, Rapoport J. Mortality Probability Models (MPM II) based on an international cohort of ICU patients. *JAMA.* 1993;270:2478-86.
[7] Wheeler AP, Bernard GR. Treating patients with severe sepsis. *N Engl J Med.* 1999;340:207-14.
[8] Todi S, Chatterjee S, Bhattacharyya M. Epidemiology of severe sepsis in India. *Crit Care*. 2007;11(Suppl 2):65.
[9] Capuzzo M, Valpondi V, Sgarbi A, Bortolazzi S, Pavoni V, Gilli G, et al. Validation of severity scoring systems SAPS II and APACHE II in a single-center population. *Intensive Care Med.* 2000;26(12):1779-85.

[10] Arabi Y, Haddad S, Goraj R, Al-Shimemeri A, Al-Malik S. Assessment of performance of four mortality prediction systems in a Saudi Arabian intensive care unit. *Crit Care*. 2002;6(2):166-74.
[11] Arabi Y, Al-Shirawi N, Memish Z, Venkatesh S, Al-Shimemeri A. Assessment of six mortality prediction models in patients admitted with severe sepsis and septic shock to the intensive care unit: a prospective cohort study. *Crit Care.* 2003;7(5):R 116-22.
[12] Robert S Munford. Severe Sepsis and Septic Shock. In: Kasper DL, Eugene Braunwald, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. *Harrison's Principles of Internal Medicine. 16th Ed. New York: McGraw-Hill;* 2005. p.1606-12.
[13] Goldhill DR, Sumner A. Outcome of intensive care patients in a group of British Intensive Care Units. *Crit Care Med.* 1998;26:1337-45.
[14] Moreno R, Morais P. Outcome prediction in intensive care: Results of a prospective, multi-centre, Portuguese study. *Intensive Care Med.* 1997;23:177-86.

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