ORIGINAL RESEARCH PAPER

Internal Medicine

PREDICTION OF OUTCOME IN PATIENTS WITH SEPSIS USING C-REACTIVE PROTEIN (CRP) AND SIMPLIFIED ACUTE PHYSIOLOGY SCORING SYSTEM 3 (SAPS3)

KEY WORDS: Sepsis, C-RP, SAPS 3 score.

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ABSTRACT

Background: Sepsis is associated with high mortality and morbidity if not recognised early. Hence scoring systems are essential to guide us regarding the initiation of treatment. Sepsis can progress to a multitude of complications and assessing the mortality is difficult without the scores.

Objectives: 1. To find whether there is a correlation between admission CRP level and outcome in patients with sepsis. 2. To find the correlation between SAPS3 and outcome in patients with sepsis. 3. To find a correlation by combining admission CRP level and SAPS3 in predicting mortality in sepsis patients.

Methods: This prospective observational study was conducted in Yenepoya Medical College from Jan 2015 to Jan 2016. 50 patients admitted to the ICU who fulfil the inclusion criteria were enrolled in the study. Serum CRP and variables to calculate the SAPS3 score were collected within 1 hour of admission. The values of CRP levels and SAPS3 score were compared, in relation to the severity and outcome of the disease.

Results: Out of 50 patients, 26 patients were male and 24 patients were female. Majority of the patients were with age group of 40-60 yrs. Mean CRP levels in patients were 67 mg/dl. Higher the CRP, prognosis was bad. CRP had sensitivity of 82% and specificity of 0 % in predicting mortality in patients with sepsis and was not statistically significant (p =.115). Mean SAPS3 score in patients were 45.3. Majority of patients expired when SAPS3 score of > 40. We observed SAPS3 score had sensitivity of 100% and specificity of 84% in predicting mortality in patients with sepsis, which was statistically significant (p .026). When we take both CRP level and SAPS3 score, we observed no correlation in predicting the mortality (statistically not significant).

Conclusion: These results suggest that SAPS3 score alone is better for predicting the mortality in sepsis, than using CRP alone or in combination.

INTRODUCTION

Sepsis, the host response to infection, involves a series of clinical, hematological, inflammatory and metabolic responses that can ultimately lead to organ failure Sepsis and MODS is a common cause of ICU mortality and morbidity with a mortality rate of 40 to 60% (1-4). The primary cause triggers an uncontrollable inflammatory response. Sepsis can progress to septic shock and Multi organ dysfunction syndrome is well established as the final stage of the continuum (5). Patients admitted to the ICU need aggressive supportive management as well as detailed investigations to reverse the cause (6). In patients where the cause is known or established within 24 hours of admission, the management is predictable, the prognosis and the outcome is favourable. In patients in whom the diagnosis is not established within 24 hours the prognosis varies from day to day. Cultures and serology are available only after several hours. In the crucial hours which determine the prognosis of the patient the physician has to depend on clinical symptomatology and demographic data to aid in diagnosis and management. Patients are often empirically treated and the management is directed towards supportive care, broad spectrum antibiotic cover, early recognition and treatment of complications, and intensive monitoring to prevent worsening of sepsis. In many patients aetiology is never determined even till death or discharge.

Several biochemical markers and clinical scoring systems have been used to assess the severity and outcome of sepsis (7). Scoring systems have been developed in response to an increasing emphasis on the evaluation and monitoring of health services. The ideal components of a scoring system are data collected during the course of routine patient management that are easily measured, objective, and reproducible. Scoring system is developed to stratify critically ill patients. More the severity of illness, higher the score. Numerous scoring systems have been developed like APACHE, MPM, MODS. The first was APACHE in 1982. The 'Simplified Acute Physiology Score' (SAPS), developed and validated in France in 1984, used 13 weighted physiological variables and age to predict risk of death in ICU patients. Like APACHE scores, SAPS was calculated from the worst values obtained during the first 24 hours of ICU admission.

In 1993, SAPS II, which includes 17 variables was introduced. In 2005, SAPS3 was created. It included 20 variables divided into three sub scores related to patient characteristics prior to admission, the circumstance of the admission, and the degree of physiological derangement within 1 hour (in contrast to the 24 hour time window in the SAPS II model) before or after ICU admission. The total score can range from 0 to 217. Acute phase reaction is a general term attributed to a group of systemic and metabolic changes that occur within hours of an inflammatory stimulus. The most important component of this response comprises the acute phase proteins, which are a heterogeneous group of plasma proteins. They are elevated in wide variety of disorders including infection, inflammation, trauma and neoplasm. CRP is the prototype of human acute phase proteins and the most frequently studied one. It has been named as C-reactive protein because it adheres to the "capsule" antigen of pneumococcus. Plasma CRP production occurs via the stimulation of IL-6 in the liver. It assists in the recognition of damaged host cells and foreign pathogens, and their removal. CRP level is increased several fold in infection.

MATERIALS AND METHODS

The current study is a prospective observational study conducted in the department of medicine, yenepoya medical college mangalore. 50 patients were included in this study who had met the inclusion criteria.

Inclusion criteria:

All above 18 years who fulfilled the criteria for sepsis (SIRS) who were admitted to the Yenepoya Medical College Hospital ICU.

Systemic Inflammatory Response Syndrome (SIRS) is defined as a condition in which a patient having any two of the following abnormal variables:

- Body temp >380 C (100.4 F) or < 360 C (96.8 F)
- Heart rate > 90 beats/min
- Respiratory rate >20 breaths /min or PaCO2 < 32mm Hg
- WBC count >12000 or < 4000 cells/cumm or >10% immature [band forms]

Exclusion criteria:
Patients requiring immediate surgical intervention. For patients with two or more admissions to the ICU during the same hospital stay, only the data from the first admission included.

METHODOLOGY

- Written informed consent was obtained from each participant or from his/her relatives
- 50 patients who fulfilled the criteria for sepsis and admitted to intensive care unit of YMCH over a period of one year were included in the study.
- A detailed history, clinical findings, and complications were recorded.
- Serum CRP level & other information required for the calculation of the SAPS3 was collected.

Methodology and Estimation of CRP

- Blood sample was collected from the patient and sent to laboratory. Serum or plasma was separated from the sample. This serum or plasma was used for estimation of CRP.
- CRP reagent was used to measure the C - reactive protein concentration by a turbidimetric method. In the reaction, C - reactive protein combines with specific antibody to form insoluble antigen- antibody complexes.
- For the SAPS3, data was recorded using SAPS 3 admission score sheet downloaded from the SAPS 3 website (http://www. saps3.org).
- The predicted mortality was estimated using both the general SAPS3 equation and also the customized equation for Australasia.
- The customized SAPS 3 score equation for Australasia is: Log it = -22.5717 + ln (SAPS 3 score + 1) × 5.3163.1

SAPS 3 ADMISSION SCORE

BOX 1

Demographic health status	
Parameters	**Scores**
Age	
<40	0
41-60	5
61-70	9
71- 75	13
76-80	15
>80	18
Co-morbidities	
Others	0
Chemotherapy	3
ICC NYHA IV	6
Hematologic neoplasia	6
Cirrhosis	8
AIDS	8
Metastasis	11
In-hospital days before ICU	
<14	0
15-28	6
>28	7
Origin	
Operating room	0
ER	5
Other ICU	7
Others	8
Vasoactive drugs	
Yes	3
No	0

BOX 2:

Diagnostic category	
Parameters	**Scores**
Schedule admission	0
Non-schedule admission	9
Urgency	
Non surgical	5
Elective	0
Emergency	6
Type of surgery	
Transplantation	-11
Trauma	-8
MR without valve	-6
Stroke surgery	5
Other	0
ICU admission add 16 points	16
Reason for admission	
Neurologic	
Seizures	-4
Coma, confusion, agitation	4
Focal defecit	7
Intracranial mass effect	11
Cardiologic	
Arrhythmia	-5
Hemorrhagic shock	3
No hemorrhagic shock	3
Distributive shock	5
Abdomen	
Acute abdomen	3
Severe pancreatitis	9
Liver failure	6
Others	0
Infection	
Nosocomial	4
Respiratory	5

BOX 3:

Physiologic parameters on admission	
Parameters	**Scores**
Glasgow coma scale	
3-4	15
5	10
6	7
8-12	2
>13	0
Heart rate	
<120	0
121-160	5
>160	7
Systolic blood pressure	
<40	11
41-70	8
71-120	3
>120	0
Oxygenation	
Mechanical ventilation pao2/fio2 <100	11
Mechanical ventilation pao2/fio2 >100	7
Without mechanical ventilation pao2/fio2 <60	5
Without mechanical ventilation pao2/fio2 >60	0
Temperature	
<34.5	7
>34.5	0
Leukocytes	
<15000	0
>15000	2
Platelets	
<20000	13
20001-50000	8
50000-100000	5

>100000	0
Ph	
<7.25	3
>7.25	0
Creatinine mg/dl	
<1.2	0
1.2-2	2
>2.0<3.5	7
>3.5	8
Bilirubin mg/dl	
<2	0
2-6	4
>6	5

DATA ANALYSIS:

- Chi Square Test for association between CRP level and patient outcome, and between SAPS3 and patient outcome.

CRP observed in the study population ranges from 20-90 mg/dl with a mean 67.09(±25.47)mg/dl. Logistic regression was done to asses CRP alone with outcome of sepsis patients using -2log likliehood (41.13), Cox & Snell R square (0.114), Nagelkarke R square (0.186) and observed sensitivity of 100% but 0% specificity. CRP was correlated with source of infection and found to have no statistical significance with outcome.

TABLE 2: COMPARISON OF OUTCOME AMONG SOURCE OF SEPSIS, SEPSIS WITH COMORBID CONDITION AND SAPS 3 SCORE:

Parameters	
Age	49.92(±13.12)
Sex Male Female	 26(52%) 24(48%)
Source of sepsis Respiratory tract infection Urinary tract infection MODS	 26(52%) 12(24%) 12(24%)
Sepsis with Diabetes mellitus Hypertension Chronic kidney disease	 26(52%) 24(48%) 12(24%)
CRP	67 (±25.47)mg/dl
SAPS 3 score 0-20 20-40 40-60 60-80 >80	 0 18(36%) 26(52%) 5(10%) 1(2%)
Outcome Improved Death	 41(82%) 9(18%)

- Logistic Regression Model to predict patient outcome using CRP and SAPS3

RESULTS AND STATISTICAL ANALYSIS

In our observational study, 50 patients with sepsis were included. Of which 26 (52%) were male and 24 (48%) were females, ranging from 19-80 years of age with a mean age of 49.9(±13.12) years. In the study population source of sepsis was respiratory tract infections, urinary tract infections or MODS. Study population was also associated with co morbid conditions like diabetes, hypertension and CKD.

TABLE 1: Baseline characteristics:

PARAMETERS	OUTCOME IMPROVED	DEATH
Source of sepsis:	22	4
Respiratory tract infections	11	1
Urinary tract infections	8	4
MODS		
Sepsis with:	19	7
Diabetes mellitus	21	3
Hypertension	11	1
CKD		
SAPS 3 score:		
20-40	18	0
40-60	18	8
60-80	5	0
>80	0	1

SAPS 3 score using Australasia equation was calculated in the study population and found to have minimum core of 24 and maximum of 89. Logistic regression was done to asses SAPS 3 score and prediction of mortality in the study population. T was observed that SAPS 3 score has 100% sensitivity and 84% specificity to the prediction of mortality and it was statistically significant (PPV- 11.11%, NPV – 100%, p = 0.026).

In the study population, SAPS 3 score of <40 has no deaths, 26 patients has a score of 40-60 of which 8 deaths were noted & 6 patients has a score of >60 of which 1 death was noted. There was no statistical significance between SAPS 3 score and source of sepsis.

There was no statistically significant correlation between CRP or CRP combined with SAPS 3score on the prediction of mortality in patients with sepsis.

DISCUSSION

There has been an improvement in the socioeconomic status and healthcare standards in the developing world. The better understanding of the medical needs, the facilities available to the common man and outcome expectations have posed a significant burden on the practicing physician, especially in dealing with critical patients. Patients in sepsis are one group of such patients who pose a challenge, as most of them have a high rate of morbidity and mortality and the diagnosis is almost never established if they succumb to sepsis early.

India also witnessing this change in social scenario, with the villager who never left his village becoming more demanding when it comes to healthcare expectations and outcomes. Above all, when the disease starts with relatively simple symptoms like fever, malaise and progresses within a matter of hours to days to sepsis, especially in the young or at times the only bread winner of the family, the prognosis needs to be communicated to the patient and relatives keeping in mind the family and social repercussions. Scoring systems have been developed to evaluate delivery of care and provide prediction of outcome of groups of critically ill patients who are admitted to ICU. The prognosis should have an evidence basis. Though there are several markers, most of them are nonspecific. The scoring systems available are mostly devised by and for the western countries. Keeping all the above in mind, we at the department of General Medicine at Yenepoya medical college decided to evaluate the newly advocated score in evaluating sepsis which was devised in a way to eliminate the demographic barriers - the Simplified Acute Physiology Scoring 3 (SAPS3). This system was developed to simplify pre-existing scoring systems like APACHE. The main advantage of this scoring system is, it allows predicting outcome before ICU intervention occurs. It is less time consuming to collect data and can have greater information which could have been otherwise missed. SAPS3 scoring system has the unique advantage of utilising tailor-made equation for different geographical regions. We used the Australasia equation of SAPS3 scoring system.

AGE DISTRIBUTION

In this present study, mean age of the study population was 49.92 years, with a range from 19 to 80 years. In the study by Jeong Am Ryu et al.8 The median age of study population was 62 years and the age ranged from 54~71 years. But, in a similar study by Surendra et al.9, the median age was 29 years and the age ranged from (24-49 years).

GENDER DISTRIBUTION

In our study, patients with sepsis were mostly males (52%).This is comparable with the following studies. In a study by Pilika K et al10 in 2015, the number of cases affected by MODS were 73 males and females were 41. In the study by Basi S et al.**11** in 2005, the

number of males were 53 and females 37. Surendra et.al9 observed that, in patients admitted with sepsis in the ICU, 60% were males. Jeong-Am Ryu et al.8 study showed that patients affected from sepsis were predominantly males (66 %), which was similar to our study.

PRIMARY SOURCE OF SEPSIS

In our study, the majority of patients had respiratory tract infections (58%) and urinary tract infections (30%). Study by Emmanuel J12 found that majority (87.5%) of the cases admitted to the ICU were medical cases, with pneumonia (25.3%) and sepsis syndrome (19%) as the most frequent primary diagnosis.

UNDERLYING PREMORBID CONDITIONS

There were 26 patients (52%) with T2DM, 24(48%) with HTN, and 12(24%) patients with CKD in our study population. In a study conducted by Harpit KM et al13 observed that out of 50 patients admitted in ICU with sepsis 16 patients had only sepsis and out of them 10 survived and 6 died. Out of 2 patients who had diabetes, 2 patients (100%) died. In 3 patients with systemic HTN, 2 (66.7%) died and 1(33.3%) survived. There is no significant difference in outcome in the presence of co morbidities. In our study, out of 8 patients admitted with only sepsis (without co morbidities like HTN, DM and CKD), 1 died and 7 survived.

With co morbidities like diabetes, hypertension and chronic kidney diseases added, out of 42 patients 34 survived. There was no significant difference in the presence of co morbidities.

MORTALITY:

In the present study, 18% patients with sepsis died in the ICU, compared to overall ICU mortality of 35.7% in the study of Rocker G et al. and 22% in the study of Vincent et al.14

COMPARISON OF CRP WITH OTHER STUDIES

Daily measurement of CRP is advocated for monitoring the sepsis patients, and may be used to guide the successful treatment and change of antibiotic93.

Normal CRP value of our lab is < 10mg/dl. The maximum CRP value in our study was 90 and minimum 20 with mean of 67.06. In our study, mean CRP value in patients who recovered from the illness was 64.26mg/dl. The mean CRP value in patients who died was 79.83mg/dl. We observed that CRP level has sensitivity of 82% and 0% specificity in predicting mortality in patients with sepsis, which is statistically not significant. Many studies have shown admission CRP is a good mortality predictor in sepsis patients admitted to ICU.(Macher H et al.15,Jensen et al.16,Kibe et al.17, Clec'h et al.18, Ruiz- Alvarezet al.19). In a study by Borges et al.20, CRP was independent risk factors for predicting survival. Study by Hoeboer et al.21, on sepsis showed that CRP is useful in judging responses to antibiotic treatment in septic patients which can indirectly affect the prognosis. Seligman et al.22 found that when the changes in the levels of CRP at onset and on the fourth day are traced, it can be a useful predictor of survival of ventilator-associated pneumonia patients. Park et al.23 showed that the CRP is more accurate in early identification of infection in patients with impaired renal function. Ho et al.24 conducted a case-control study that included 12 patients re-admitted to the ICU and observed a significant association between CRP levels and re-admission.

In another study by Devran O et al.25 it was shown that the CRP concentrations were higher in non-survivors than survivors (105 mg/L vs. 44 mg/L) after the 3rd to 5th day of treatment. CRP levels helped predicting the prognosis. A prospective cohort study in 2010 by Hillas et al.26 with 45 patients found that evaluating CRP helped in predicting progression to septic shock and 28-day mortality. Work done by Ho et al.24 Hogarth et al.27 and Cox et al.28 also showed that the admission CRP value was significantly elevated in patients with sepsis who died and have concluded that high CRP level is a good predictor of poor outcome in patients with sepsis.

Moreno Calcagnotto dos Santos et al29 showed that readmitted critically ill patients exhibited worse outcomes during hospitalization which could be predicted by parameters like C-reactive protein. Agarwal et al30 not only observed an elevated CRP levels on admission in patients with sepsis, but also there was a significant and serial increase in the CRP levels in patients who later deteriorated and expired. Whereas, the patients who recovered and got shifted out of ICU to their wards showed a maximum rise until D2-D3, after which the values showed a decreasing trend, though they still often remained elevated over normal values for several days. However, studies done by Jeschke et al.31, Silvestre et al.32 and Pettila et al.33 have found that CRP level does not vary significantly in patients with sepsis who die compared to those patients who recovered from the illness, and have also concluded that the CRP is a poor prognostic marker for the prediction of outcome of patients with sepsis. Al-Subaie et al.34 observed that CRP levels on the day of ICU discharge were not predictive of readmission or unexpected death. In our study, CRP levels also did not significantly predict outcome when considered in subsets with different primary source of infections or premorbid conditions.

COMPARISION OF SAPS3 WITH OTHER STUDIES

The present study showed an increase in death rate with higher SAPS3 score. In our study, the minimum SAPS3 admission score was 24 and maximum was 89, with a mean of 45. In a study by Moreno RH et al.35, the minimum value observed was 5, and the maximum 124, with a mean of 49.9. Regarding prediction of mortality in our study, when SAPS3 score was 24, predicted mortality was 1% and when SAPS3 score was 89, predicted mortality was 84%. The mean predicted mortality was 19.8%.

Hospital mortality was greater in patients with higher SAPS3 scores. ICU mortality of 0% was observed in patients with SAPS3 score <40, increasing to around 80% in patients with SAPS3 scores 40 and 60. In a similar study by Sakr Y et al.36 which included 1851 patients, hospital mortality of <3% was observed in patients with SAPS3 scores <40, increasing to around 10% in 65 patients with SAPS 3 scores between 40 and 60. Around 70% mortality was observed in patients with a SAPS score >80. Jeong-Am Ryu et al.8 showed that patients with higher SAPS3 score also predicted higher mortality.

In our study, the sensitivity of SAPS3 in predicting mortality in sepsis patients (total group) is 83.67% and specificity is 100% which is statistically significant. However, SAPS3 scores did not significantly predict outcome when considered in subsets with different primary source of infections or premorbid conditions.

COMPARISON OF CRP AND SAPS3 / OTHER ICU SCORING SYSTEMS TOGETHER

In our study when CRP and SAPS3 score was taken together to predict mortality in patients with sepsis, we observed no statistically significant correlation. Surendra et al.9 showed that, Simplified Acute Physiology Score and CRP are independent predictors of mortality in predicting 28-day mortality, higher CRP (CRPc) clearance were significantly associated with treatment failure ($p = 0.027$ and $p = 0.030$, respectively) and marginally significant in predicting 28-day mortality. In study by Agarwal et al.30, CRP levels were compared with SOFA scores and concluded that CRP levels greater than 100 mg/L on the third day in the ICU are equivalent to high SOFA scores as predictor of mortality in patients with sepsis. Deepak C L37 reported that mean CRP value in patients who recovered from the illness was 140.6 mg/dl and in patients who died was 191.1 mg/dl. CRP level of > 137 mg/dl, had sensitivity of 60% and specificity of 60% in predicting mortality in patients with sepsis and was not statistically significant. Mean APACHE II score in patients who died was 24.2, compared to the patients who recovered was 18.5 (p .002). It was concluded that it is better to combine both CRP and APACHE II for predicting the mortality in sepsis patients, than using either of them. Agarwal et al.30 have observed that APACHE II scoring system underestimates the mortality. So, they opined that isolated APACHE II score is a poor predictor of mortality when used alone and it would be better if combined with other parameters, such as CRP levels. However, in our study SAPS3 scoring system alone was a good tool in predicting mortality.

SUMMARY

The study was a prospective observational study conducted over a period of one year from January 2015 to January 2016 on 50 consenting patients with sepsis who were admitted to the intensive care unit, who satisfied the pre-defined criteria. The study focused on the utility of newer ICU scoring systems in predicting outcome in patients with sepsis. We made the following observations:

- Patients admitted with sepsis to the ICU were mainly males 52%.
- The mean age in our study population was 49.7 years.
- Higher the SAP 3 score, higher was the mortality
- Higher the CRP values indicated poor prognosis, though statistically insignificant.
- The severity of organ dysfunction proved to be a good marker in discriminating outcome in patients with severe sepsis.
- The SAPS3 scores showed high accuracy in predicting outcome, thus highlighting the multiple organ involvement in sepsis patients.
- Evolving organ dysfunction following admission to the ICU strongly affected the outcome.
- SAPS3 scores alone were better in predicting outcome
- compared to CRP alone or combined.
- The assessment of organ dysfunction should be used to early risk stratification in clinical trials including critically ill patients with severe sepsis

CONCLUSIONS

- SAPS3 scoring system has the unique advantage of utilising tailor-made equation for different geographical regions.
- SAPS3 score can be used to predict the outcome in ICU patients with sepsis.
- The SAPS 3 score correlated well with the mortality.
- The SAPS3 score can be a useful tool to the ICU physician in selecting patients for ICU care, monitoring their clinical condition, assessment of organ dysfunction and predicting mortality.
- Serial SAPS3 score monitoring will also help the physicians for transferring patients from the ICU and thus proper utilization of scarce ICU resources in developing countries like ours.
- Further studies in larger number of patients, serial measurement of variables and comparison between different scoring systems will help to improve the accuracy of scoring systems like SAPS3.

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