JIHS The Journal of Integrated Health Sciences

Available online at www.jihs.in

Original Article

Study of various prognostic factors for sepsis patients requiring intensive medical care with special emphasis on APACHE II score in prognostication

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ABSTRACT

Background: Sepsis has remained a leading cause of bed occupancy and mortality in medical ICU around the world. There is limited epidemiological information from south Asian countries about the prognostic factors for the outcome in such patients which is very important in planning for treatment strategies.

Aim: We investigated various prognostic factors for sepsis and also the use of APACHE II scoring system as a prognostic tool.

Methodology: We analysed 50 patients with sepsis admitted to medical ICU. All demographic, etiological, clinical and investigatory parameters were recorded and APACHE II score was calculated for all patients on the day of admission. Patients were followed till discharge or death in hospital.

Results: Among wide range of primary diseases causing sepsis in our study, tropical sepsis was one of the major contributors which differ from the western studies. Overall mortality was 28% which is comparable to other parts of the world. Demographic profiles including sex, area of residence and socio-economic status except increasing age did not correlate well with mortality in sepsis patients. Central nervous system and respiratory system involvement led to highest mortality (52%). Number of organ systems involved was found to be statistically significant predictive factor for mortality in severe sepsis ($p < 0.05$). Mean APACHE II score of study patients was 22.84 ± 7.57. Severity grading of sepsis as per APACHE II scoring system correlated very well with mortality ($p < 0.05$) but it did not correlate with length of ICU stay.

Conclusion: In the era of many complex scoring systems, along with traditional prognostic factors, age old APACHE II scoring system is still a very user-friendly and inexpensive method which can be used at the bedside for mortality prediction in sepsis patients.

Key words: Sepsis, Multi Organ Dysfunction, APACHE II scoring system.

INTRODUCTION

Sepsis is one of the most important causes of death in medical care units worldwide. There are more than 750000 cases of sepsis per year in the USA and more than 200000 deaths per year entitled to this entity.[1] The mortality in septic shock is from 40 to 60 percent despite the intensive care provided to these patients.[1]

Sepsis & septic shock commonly follow gram-negative bacterial infections. There is however, an increasing incidence of gram-positive infections producing septic shock.[2] The use of broad-spectrum antibiotics over prolonged periods of time and organ transplantation has brought in the fungal and viral infections which can also produce the picture of severe sepsis and septic shock.[3] The incidence of sepsis and septic shock appears to be increasing all over the world. Inadequate immune responses to infection due to underlying diseases such as malignancy, lymphomas, leukaemia, HIV infection, chronic kidney disease, diabetes etc. predispose to sepsis and septic shock. Infections in the elderly and in the malnourished are also frequently followed by severe sepsis, septic shock and death. Iatrogenic

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infections induced by procedures or their complications in critical care units can also cause septic shock.[4,5] However sepsis and septic shock occurring from community-acquired infections outnumber sepsis and septic shock due to nosocomial infections.[1]

Sepsis is associated with high level of mortality and morbidity and it poses great economical burden to the individual and the community. It continues to be one of the major problems confronting consultants. Despite the many advances in antimicrobial agents and supportive care, mortality from sepsis remains unacceptably high. Patients with sepsis are among the most complex patients encountered in medical practice. This complexity is due to varied etiologies and variable prognosis. Thus, there is a need in this group of patients for the usage of mortality prediction models to provide patients a quality care and also to utilize available resources optimally.

Over the past few decades several scoring models like APACHE, SAPS, MPM, MODS, ODIN, SOFA, CIS, etc have been developed for predicting outcome of admitted sepsis patients. Utilization of scoring system has been suggested to result in management decisions that could salvage costly ICU resources scantily available in developing world. APACHE-II scoring system has been used to predict ICU mortality since many years. Many studies have acknowledged utility of APACHE-II scoring in selection of patients for ICU admission and in provision of optimal management of sepsis patients.

The data available till date mostly represents the western world trends. Clinical and investigatory profiles of patients from the developing countries like India tend to differ from that of western world due to difference in the environmental, social, cultural and economical diversities. Realizing the utility of APACHE-II scoring system in mortality prediction in critically ill medical patients, the present study was undertaken to evaluate the etiological, clinical, and investigatory profile and the performance of APACHE-II score in prediction of risk of mortality in patients with sepsis admitted to medical ICU of a tertiary care hospital.

METHODOLOGY

The prospective cross sectional study was conducted in department of medicine, SBKS MI & RC, Piparia, Vadodara after approval from Institutional Ethics Committee. A total of 50 consecutive patients fulfilling sepsis criteria defined by Society of Critical Care Medicine consensus panel (Table 1) admitted in medical ICU between July 2011 to Oct 2012 were enrolled in the study after obtaining written and informed consent. Patients developing sepsis post operatively or because of primary surgical event were excluded from the study.

Table 1. SIRS, Sepsis, MODS definitions

Systemic inflammatory response syndrome (SIRS)	Two or more of the following conditions: (1) Fever (oral temperature >38°C) or hypothermia (<36°C); (2) Tachypnea (>24 breaths/min); (3) Tachycardia (heart rate >90 beats/min) (4) Leukocytosis (>12,000/μL), leucopenia (<4,000/μL), or >10% bands; may have a noninfectious etiology
Sepsis	SIRS that has a proven or suspected microbial etiology.
Multiple-organ dysfunction syndrome (MODS)	Dysfunction of more than one organ, requiring intervention to maintain homeostasis

(Taken from the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.)[6]

Besides demographic data, detailed history of presenting as well as past illness, general and systemic examination was carried out on the day of admission. All relevant investigations as per primary aetiology, severity of disease, organ system involvement, complications and other associated co morbidities were also carried out at the central laboratory. If the primary source of infection was not obvious, blood culture was performed. All the information was recorded in prescribed Case Record Forms.

Table 2. Acute Physiology and Chronic Health Evaluation II[7]

ACUTE PHYSIOLOGY SCORE (a)									
Score	**4**	**3**	**2**	**1**	**0**	**1**	**2**	**3**	**4**
Rectal Temp,˚C	41	39.0-40.9		38.5-38.9	36.0-38.4	34.0-35.9	32.0-33.9	30.0-31.9	29.9
Mean blood pressure, mmHg	160	130-159	110-129		70-109		50-69		49
Heart rate	180	140-179	110-139		70-109		55-69	40-54	39
Respiratory rate	50	35-49		25-34	12-24	10-11	6-9		5
Arterial pH	7.7	7.60-7.69		7.50-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
Oxygenation									
If Flo_2>0.5, use (A-a) Do_2	500	350-499	200-349		< 200				
If Flo2 0.5, use Pao_2					> 70	61-70		55-60	< 55
Serum sodium, meq/L	180	160-179	155-159	150-154	130-149		120-129	111-119	110
Serum potassium, mg/dL	7	6.0-6.9		5.5-5.9	3.5-5.4	3.0-3.4	2.5-2.9		< 2.5
Serum creatinine, mg/dL	3.5	2.0-3.4	1.5-1.9		0.6-1.4		< 0.6		
Hematocrit	60		50-59.9	46-49.9	30-45.9		20-29.9		< 20
WBC count, 10^3/mL	40		20-39.9	15-19.9	3-14.9		1-2.9		< 1

GLASGOW COMA SCORE (b)			
Eye opening	**Verbal (Nonintubated)**	**Verbal (Intubated)**	**Motor Activity**
4-Spontaneous	5-Oriented and talks	5-Seems able to talk	6-Verbal command
3-Verbal stimuli	4-Disoriented and talks	3-Questionable ability to talk	5-Localizes to pain
2-Painful stimuli	3-Inappropriate words	1-Generally unresponsive	4-Withdraws to pain
1-No response	2-Incomprehensible sounds		3-Decorticate
	1-No response		2-Decerebrate
			1-No response

POINTS ASSIGNED TO AGE AND CHRONIC DISEASE AS PART OF THE APACHE II SCORE (C)					
Age, years	< 45	45-54	55-64	65-74	75
Score	0	2	3	5	6

HISTORY OF CHRONIC CONDITIONS (d)	
Chronic health	**Score**
None	0
If patient is admitted after elective surgery	2
If patient is admitted after emergency surgery or for reason other than after elective surgery	5

a) APACHE II score is the sum of the acute physiology score (vital signs, oxygenation, laboratory values), Glasgow coma score, age, and chronic health points. Worst values during first 24 hours in the ICU should be used

b) Glasgow coma score (GCS) = eye-opening score + verbal (intubated or nonintubated) score + motor score.

c) For GCS component of acute physiology score, subtract GCS from 15 to obtain points assigned.

d) Chronic health conditions: liver cirrhosis with portal hypertension or encephalopathy; cardiovascular, class IV angina (at rest or with minimal self-care activities); pulmonary, chronic hypoxemia or hypercapnia, polycythemia, ventilator dependence; kidney, chronic peritoneal or hemodialysis; immune, immunocompromised host.

Note: (A - a) D_{O2}, alveolar-arterial oxygen difference; WBC, white blood (cell) count

Severity of disease was graded according to APACHE II scoring system within first 24 hours of admission (Table 2). In calculation of the score, the worst values for each parameter in first 24 hours period were used. The patients' score was counted from maximum score of 71. Patients were followed till hospital discharge or death. The results were presented as mean (SD). X^2 test was used to evaluate the statistical significance of categorical variables and P value <0.05 was considered significant.

Table 3. Patients' demographic characteristics

Patients' characteristics	Groups	n(%)	Death(%)	P value
Age (in years) (Mean Age: 48.76 ± 19.79)	18 – 35	16(32%)	5(31.3%)	**0.0004**
	36 – 60	18(36%)	6(33.3%)	
	>60	16(32%)	3(18.8%)	
Sex	Male	28(56%)	8(28.6%)	**0.029**
	Female	22(44%)	6(27.3%)	
Residence	Urban	21(42%)	5(23.8%)	0.056
	Rural	29(58%)	9(31%)	
Socio-Economical Status (SES)	Upper	0	0	0.242
	Middle	27(54%)	6(22.2%)	
	Lower	23(46%)	8(34.8%)	
Addiction	Tobacco chewing	5(10%)	1(20%)	
	Smoking	4(8%)	0	
	Alcohol	5(10%)	2(40%)	

RESULTS

The study involved 50 consecutive sepsis patients admitted to medical ICU. The study population comprised of all age group patients with mean age of 48.76±19.79 years. 56% of patients were male and 58% were from rural area. All patients were from lower or lower - middle socio economical class. (Table 3)

Clinical profile

Clinical presentation of study patients varied widely with respect to primary diseases causing sepsis, severity of primary diseases, number of organ systems involved, predominance of systems involved, and organisms responsible for sepsis. The most common symptoms on presentation were fever, breathlessness, abdominal pain, vomiting and other symptoms according to primary causes.

Diverse primary conditions leading to sepsis were noted in the study. Most common disease leading to sepsis in this study was community acquired pneumonia (24%). Other diseases leading to sepsis were malaria, chronic kidney disease, cerebro-vascular stroke, sickle cell anaemia, organo-phosphorus poisoning, dengue fever etc. Interestingly, tropical infections were found as one of the major causes of sepsis and Multiple Organ Dysfunction Syndrome (MODS) in this study. Out of 50 patients, 32% had tropical infections such as malaria, dengue fever, leptospirosis as primary diseases leading to sepsis (Table 4).

Table 4. Frequency of tropical sepsis* and related mortality

Diseases	N (%)	Death (%)	P value
Tropical	16(32%)	4(25%)	0.198 (>0.05)
Nontropical	34(68%)	10(29.4%)	

**(Tropical sepsis was defined as sepsis due to infections prevalent in Tropical region)*

Once sepsis was suspected, blood culture and sensitivity were done within 24 hours of admission to the hospital before starting the treatment for all study patients. Out of 50 patients, only 12 (24%) patients had positive blood culture report. Most common organisms were pseudomonas, klebsiella and E.coli.

Among the study patients, two most commonly

involved organ systems were renal (78%) and hematology (62%). Frequency of involvement of all other organ systems was almost similar (40 to 46%). Greater mortality was seen with CNS (27.3%) and respiratory (26.1%) system involvement, followed by liver (15%) and CVS (15%). Surprisingly, patients with most commonly involved organ systems haematology and renal showed least mortality, 12.9% and 12.8% respectively. (Figure 1) Overall, 32(64%) patients had severe MODS in the form of three or more organ systems involvement having higher mortality (92.9%). 36% patients having one or two organs involvement showed very less mortality (7.1%) (Figure 2).

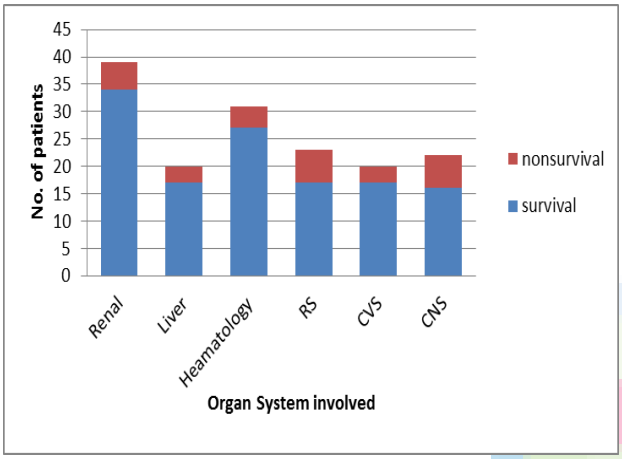

Figure 1. Frequency of various organ system involvements

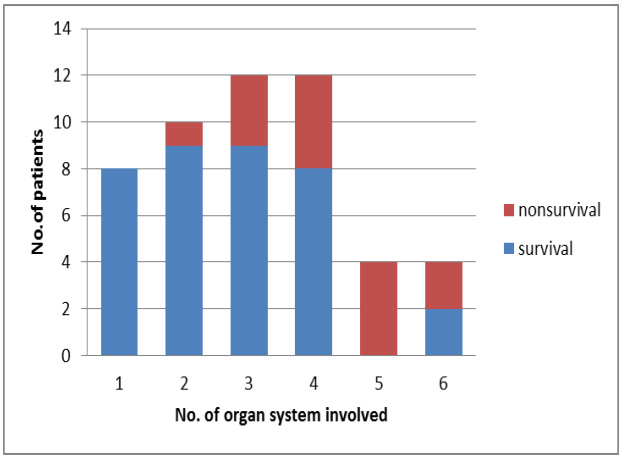

Figure 2. Number of total organ systems involved

Mean APACHE II score of the study patients was 22.84 ± 7.57. Mean APACHE II score of survivors was 20.69 ± 6.33, while that of non survivors was 28.35 ±7.46. Only 6 (12%) patients had APACHE II score less than 14 indicating mild sepsis. All these patients had good outcome. Most of the patients had moderate severity with APACHE II score between 15 and 29 (68%), showing average mortality of 24.6%. 10 patients had severe sepsis, having highest mortality of 60%. So as the APACHE II score increased the severity of sepsis and mortality also increased (Table 5).

Table 5. APACHE II Score grading[8] and its relation to mortality

Score	Grade	N (%)	Death (%)	P value
0 – 4	I	0	0	
5 – 9	II	1(2%)	0	
10 – 14	III	5(10%)	0	
15 – 19	IV	13(26%)	2(15.4%)	**0.025**
20 – 24	V	9(18%)	3(33.3%)	(<0.05)
25 – 29	VI	12(24%)	3(25%)	
30 – 34	VII	7(14%)	3(42.8%)	
over 34	VIII	3(6%)	3(100%)	

DISCUSSION

Sepsis represents substantial healthcare burden and there is limited epidemiological information about demography of sepsis, MODS and mortality prediction in such cases from South Asian region. Previous reports from various studies noted a substantial increase in incidence of number of death attributed to sepsis despite decline in overall hospital mortality and sepsis is now among the ten leading causes of death in the United States[9]. The possible explanation is that as sepsis is becoming more familiar, it may have been more commonly recognized or more readily coded into medical records. The other possible reason for real increase in the incidence of sepsis includes the increased use of invasive procedures and immunosuppressive drugs, chemotherapy and transplantation, the emergence of the epidemic of HIV infection and increasing microbial resistance.[10]

Contradictory to above findings, the declining mortality is notable in few studies giving due attention to the expected increasing age and the increasing severity of illness. Such changes are more likely attributed to improvements in intensive care treatment.[11,12] The overall mortality in this study is

28% which is quite comparable with studies from Western and East Asian countries.[13,14] The studies from Indian subcontinents have shown high mortality (54.2% by Naved et al. (2011), 48% by Desai et al. (2013), 59.3% by Todi et al. (2007)).[15-17] Compared to these studies, this study has less mortality, may be because of well-equipped ICU set up, aggressive management, continuous monitoring with vigilant standardized aseptic precautions and proper nursing care at state of art ICU.

Most of the available data regarding demography scoring and mortality related to sepsis and MODS are from western countries. India has diverse life style pattern, cultural, rituals, ethnic variation, and tropical and subtropical climate in most of the regions, so epidemiological profile and primary etiologies for sepsis and MODS may differ from the western countries. There are very few Indian data available for sepsis and various scoring systems for mortality prediction in such patients.

Mean age of patients in this study was 48.76 ± 19.79 years (ranging from 18 to 92 years) which is slightly lower than many other studies[15,17]. In the present study, highly significant ($p<0.001$) association between age and outcome was observed. Angus DC et al from United states[19] and Naved et al. (2011) from Pakistan also demonstrated increase in mortality with increasing age[15]. As, this hospital receives patients from peripheral and remote village area; more number of patients are from rural area (58%) and middle (54%) and lower (46%) socio economical class. The mortality was more in rural as well as lower socio-economical class patients but the difference was not statistically significant ($p>0.05$). The reason for higher mortality may be low education level, adverse financial conditions and late initiation of treatment.

Primary diseases leading to sepsis in this study vary widely. Most common primary aetiology leading to sepsis was community acquired pneumonia (24%) followed by malaria (18%) and chronic renal disease (14%). Tropical diseases are major contributors to the study groups. 32% of the study patients were having tropical diseases like malaria, dengue fever and leptospirosis as primary aetiologies for sepsis (Figure 3), so this study highlights the geographical difference in causes of sepsis and identifies tropical sepsis as one of the leading reason for utilization of medical intensive care services in this region. Malaria was found to be most common cause of sepsis in MICU by Desai et al. (2013)[16] Mortality rate in tropical sepsis patients was found to be lower than non tropical causes, but difference was not statistically significant ($p>0.05$). Clinical presentations in this study vary widely as per primary diseases causing sepsis, severity of primary diseases, number of organ systems involved, predominance of systems involved, and organisms responsible for sepsis and severity of sepsis. Most common SIRS criteria found to be abnormal was WBC counts, which can be considered as one of the integral finding of sepsis. Surprisingly, all other three criteria – temperature, pulse and respiratory rate were abnormal only in around half of the patients. This observation of the study highlights that vital signs might be normal in sepsis even in the patients who are critically ill.

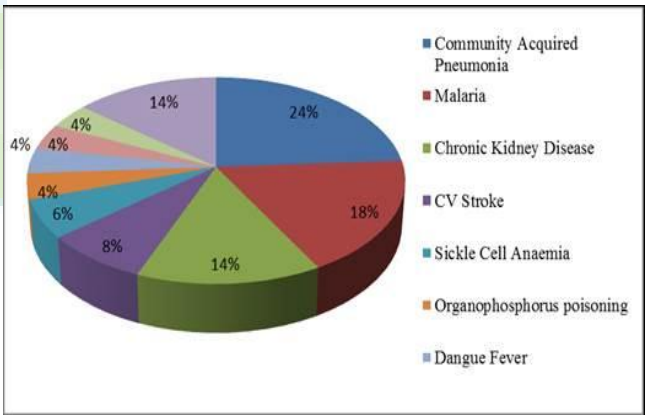

Figure 3 Primary diseases leading to sepsis

In this study, renal dysfunction and haematology dysfunction, mainly in the form of platelet dysfunction were most common as compared to all other organ dysfunction which is a quite different finding from many other studies which had shown cardiovascular dysfunction as commonest dysfunction,[13,20] while study from the similar geographical area found lung to be involved most commonly[16]. In this study, mortality correlated more with central nervous system and respiratory dysfunction, (Figure 2) while Umegaki et al. (2011) had shown hepatic dysfunction as a strong factor for

the ICU death in such patients[13]. The striking observation made in this study is that the increasing death rate correlated with the number of organ dysfunction involved with no relation to the combination of organ dysfunction (Figure 3). Similar results were also reported by various other researchers[13,20,21]. Number of acute organ dysfunction is a useful prognostic indicator for ICU mortality in critically ill sepsis patients.

Altered levels of haemoglobin, platelet count, blood sugar, creatinine, total bilirubin and blood pH were significantly associated with adverse outcome ($p<0.005$), while higher or lower WBC count did not correlate statistically with mortality ($p>0.005$). Only 24% of the patients had positive blood culture report. Sands et al had also shown similar report.[22]

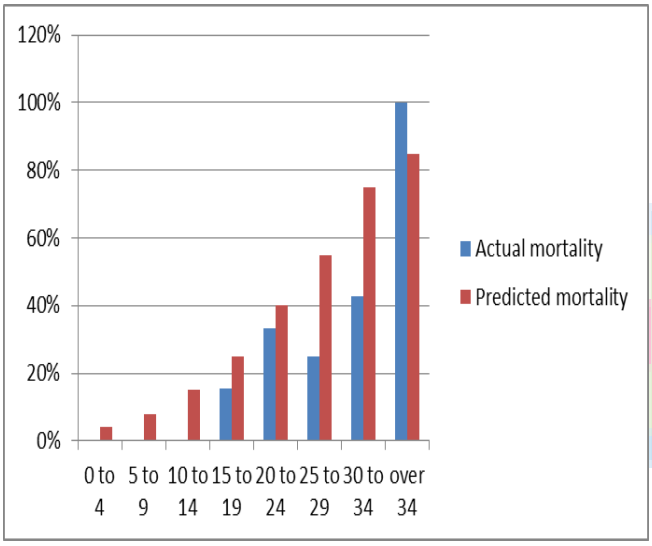

Figure 4. Comparison between Predicted and Actual mortality by APACHE II Score

Due to limited health resources and increase in the cost of health management, prediction of the prognosis of the disease has become very important area of health science. Many scoring systems have been developed for Intensive Care Unit to provide gross estimates for mortality risk in ICU patients. In this study, well accepted APACHE II scoring system has been used for mortality prediction. Mean APACHE II score of study patients is 22.84 ± 7.57, which is almost similar to other studies from same continents; 20.84 in Naved et al. (2011)and 21.5 in study by Lee et al. (1994)[15,25], while it is higher than studies from western counterparts[18,24]. The reason of high APACHE II score observed in this study was late presentation to ICU in severely ill condition for management as most of the patients were referred ones and many were having educational, social and financial barriers. In addition, APACHE II score was significantly higher in those who died [non-survival (28.35 ± 7.46), survival (20.69 ± 6.32)]. Similar findings were observed by Samir D et al from the western India[16]. In each APACHE II score interval; the mortality rate was almost similar or slightly higher than that of preceding interval except interval VI. These findings are comparable with Naved et al. (2011), Oh TE et al. (1993) and Knaus et al. (1986) [15,23,24]. The results of this study also show statistically significant association between APACHE II score and the risk of mortality (Table 5). This study has demonstrated that higher APACHE II score correlates well with mortality prediction and these mortality figures in the different score groups compare favourably with the predicted mortality, confirming the capability of this scoring system to stratify patients' prognosis according to the degree of severity of disease, which can serve as a standard for intensive care outcome, though there is a slight underestimation of mortality prediction in our population in all ranges of APACHE II scores (Figure 4). The possible explanation for this contradiction is the different primary aetiologies leading to sepsis in this study.

Length of ICU stay is the most important determinant of cost of therapy and resource utilization in resource limited countries. In this study, mean ICU stay of patients is 9.9 ± 6.21 days. Length of ICU stay does not show statistically significant correlation ($p >0.05$) with APACHE II score of patient. But our study suggests that patients with very low or very high APACHE II score have less ICU stay as they have milder or severe form of disease respectively. This information is important given the social and financial implications for often resource poor, affected persons. Use of APACHE II scoring system for mortality prediction may influence the most appropriate treatment strategy to be offered to the patients. In patients with very high mortality, very aggressive therapy might be of little benefit due to their imminent, inevitable mortality. Other way

round, we can reduce the burden of unnecessary ICU admissions and bed occupancy for the patients having low mortality prediction, sparing the same for more needy patients. Yet further data is required to generate more information on the balance of cost versus benefit in such group of patients.

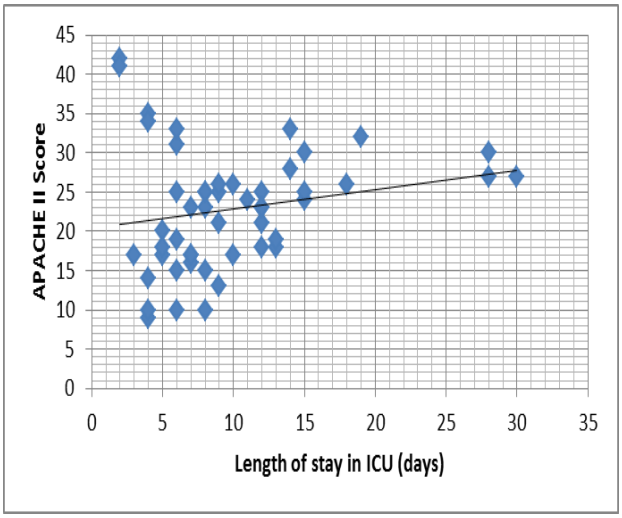

Figure 5. APACHE II Score and its relation with length of ICU stay

CONCLUSION

Sepsis is associated with high level of mortality and morbidity and it poses great economic burden to the individual and the community. Tropical sepsis is one of the important causes of the severe sepsis in Indian scenario. Though primary aetiology & its severity, many biochemical parameters, and organ system involvement shows positive correlation with mortality prediction there is always a need for a specialized though simple method for the same. APACHE II is an inexpensive user friendly scoring system since its discovery which can be applied to quantify the severity of illness and as outcome predictor even in resource limited medical centres.

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