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Original Research Article

PROGNOSTIC VALUE OF APACHE II SCORE, SOFA SCORE AND BIOMARKERS IN PATIENTS OF SEPSIS AND SEPTIC SHOCK – A COMPARATIVE STUDY

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Abstract

Background: This study investigated and compared prognostic value of Apache II score, SOFA score and the prognostic biomarkers in patients of sepsis and septic shock. **Materials and Methods:** A prospective observational study was conducted in the department of anaesthesiology, IMS BHU after approval from the hospital research and ethical committee. The study included 100 patients of age group 18 – 65yrs who met the established criteria of severe sepsis and septic shock. Patients were estimated for APACHE II and SOFA scores at the time of admission and a sample for biological markers was sent within 24 hours of admission, on the day 7, again the SOFA score was calculated and a repeat sample for biomarkers was send. Response to treatment was monitored and clinical outcomes were noted based on ICU stay. **Results:** On day 1, the APACHE II score is 17.6230 ± 4.12 and 18.0256 ± 3.88, SOFA score is 6.26 ± 1.55 in survivors and 6.35 ± 1.512 in non-survivor. While biomarkers PCT- 10.95 ± 13.99 and 13.62 ±15.88, IL-6–61.99 ± 41.25 and 86.38 ±38.81, TNF-α 16.07±3.08 and16.54 ±3.43, LACTATE- 4.51 ±1.63 and 5.03 ±1.49, S. Ferritin 1161.94 ± 1228 and 1637 ± 1637 in survivor and non-survivor respectively. In terms of mortality predictor PCT, IL-6, and S. ferritin shows more significant variability among diseased and survivors. On day 7, SOFA Score was 3.88 ± 1.05 and 9.025 ± 1.18 while PCT-2.43 ± 2.08 and 37.18 ± 13.47, IL-6- 17.10 ± 6.45 and 110.62 ± 13.20, TNF-α - 11.42 ± 2.84 and 17.07 ± 3.58, LACTATE- 3.19 ± 1.33 and 6.53 ± 3.48 and S. FERRITIN - 370.70 ± 241 and 1111.84 ± 956 in survivor and non-survivor. **Conclusion:** Our study concluded that the combined approach of various biomarkers and scoring system shows good outcome in predicting mortality in sepsis and septic shock patients than a single biomarker. Also, this approach is superior to scoring system approach alone i.e SOFA score.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection. Organ dysfunction is attributed to inflammatory injury, which is the result of uncontrolled inflammation or inadequate host defenses against inflammatory injury. There are three clinical forms of response to infection: sepsis, severe sepsis, and septic shock.[1] They are differentiated by the presence and degree of the intensity of cardiovascular dysfunction resulting from the extensity of the inflammatory response.[2]

The Third International Consensus (Sepsis-3) currently defines sepsis as "organ dysfunction caused by a dysregulated host response to infection", emphasizing for the first time the crucial role of the innate and adaptive immune response in the development of the clinical syndrome.[3]

Current sepsis guidelines recommend that the administration of antimicrobials should be initiated as soon possible because any delay in effective anti-microbial therapy may decrease survival. One of the fundamental principles for the appropriate management of sepsis is the timely identification of high-risk patients, which can be done by the application of scoring systems and plasma biomarkers. Sepsis biomarkers are useful to monitor the evolution of infectious processes, also used as prognostic and follow-up indicators.[4-5]

Sepsis-related Organ Failure Assessment (SOFA) is a prognostic score used in mortality prognosis for

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patients admitted to medical and surgical ICUs.[6] Giamarellos-Bourboulis et al.[7] have proposed a new prognostication rule for predicting the outcome of sepsis by APACHE II score. The APACHE-II (Acute Physiology and Chronic Health Evaluation II) system is validated to establish prognosis at the time of admission of critically ill patients.[6]

In the activated innate immune response to sepsis, pro-inflammatory and anti-inflammatory mediators such as tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6) and monocyte chemoattractant protein 1 (MCP-1) are released, followed by a rise in the levels of acute phase proteins such as procalcitonin, calprotectin, pro-adrenomedullin, pentraxin-3, and C-reactive protein (CRP).[8] Proinflammatory cytokines such as interleukin-Iβ (IL-lβ), tumor necrosis factor-α (TNF-α) and IL-6 may increase ferritin synthesis.[9]

As a biomarker, procalcitonin (PCT) has been found to have good specificity to distinguish bacterial from non-bacterial inflammations. IL-6 helps control the induction of the acute-phase response and also is a mediator for immunoglobulin class switching.[10] IL-6 functions as an important and sensitive indicator of inflammation within the body. IL-6 is a biomarker that acts as both pro-inflammatory cytokines as well as anti-inflammatory cytokines and is associated with the severity of organ dysfunction.[11] IL-6 is also reported to be present in the plasma earlier than the C-reactive protein.[12]

During infection, ferritin is produced by macrophages as a result of interleukin (IL)–1 and tumour necrosis factor-α induced nuclear factor kappa B (NFκβ) activation, sequestering iron from iron-loving bacteria and also preventing oxidative damage to host macrophage DNA. However, ferritin can also participate in pathobiologic macrophage activation.[13]

In human beings, the role of TNF-α in sepsis is quite debatable. TNF-α, or elevations of TNF-α, in serum or cerebrospinal fluid, have been detected in patients with serious bacterial infections, sepsis, or septic shock.[14]

Serum lactate level as a clinical tool was described approximately half a century ago by Broder and Weil.[15] Increased serum lactate level may represent tissue hypoperfusion associated with signs of organ dysfunction in critically ill patients. In addition, it is of note that the serum lactate cut-off level was decreased from 4 to 2 mmol/L. At that time, serum lactate level >4 mmol/L was associated with shock status. Since the cut-off value of serum lactate level was decreased to 2 mmol/L, serum lactate level is a more sensitive marker for septic shock.[16]

We hypothesized that biomarkers have a better prognostic value than APACHE II and SOFA scores in patients with sepsis.

MATERIALS AND METHODS

This Prospective observational study was carried out in Sir Sunderlal ICU, Department of Anaesthesiology, Sir Sunderlal Hospital, BHU, Varanasi for a duration of 18 months. 100 patients of the age group of 18-65 years who had symptoms of sepsis and septic shock, reporting at Sir Sunderlal Hospital BHU, Varanasi were included in the study. After the approval from the Institutional Ethical Committee, nature of the study was explained to the participant and a written consent was obtained. Name and other identity of the patients was not disclosed anywhere in the study.

Patients of both the genders having sign and symptoms of sepsis and septic shock were included in the study. Patients not giving consent, patients already on antibiotics and immunosuppressants, Patients of acute coronary syndrome, acute stroke, and acute pancreatitis, Pregnant and breastfeeding females were excluded from the study.

Detailed history taking, thorough physical examination and baseline investigations were done. APACHE II and SOFA scores were estimated at the time of admission in all patients having signs and symptoms of sepsis and septic shock. Following this, a sample for biological markers was sent within 24 hours along with CBC, LFT, and RFT. Concomitantly, blood culture, urine culture, and ETT aspirate (intubated patients) were sent for the microbiological outcome of investigations. On day 7, the SOFA score was again calculated and the sample for biomarkers was repeated. Response to treatment was monitored and clinical outcomes were noted based on ICU stays. The cases were followed till, discharge or Shift to the parent unit, or till expired.

The data obtained from the study were subjected to statistical analysis using SPSS version 20.0, for further evaluation at the significance level of p-value of 0.05. The data were presented as Mean ± standard deviation for continuous variables and frequency for categorical variables. For categorical data, Chi-square statistical analysis was done and for continuous data student's t-test was performed.

RESULTS

Table 1: Distribution of patients according to mortality

MORTALITY	FREQUENCY	PERCENTAGE
Survivor	61	61
Expired	39	39
Total	100	100

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Table 2: Mean value of score at day 1 and correlation of score with mortality

Score	Sepsis survivor (n=61)		Sepsis non-survivor (n=39)		Statistical analysis	
	Mean	SD	Mean	SD	t-test	p-value*
APACHE II SCORE	17.6230	4.12781	18.0256	3.88985	1.19	1.007
SOFASCORE	6.2623	1.55886	6.3590	1.51288	1.259	0.916

***p-value>0.05 is insignificant**

Table 3: Mean value of biomarkers at day 1 and correlation of biomarkers with mortality

Biomarkers	Sepsis survivor (n=61)		Sepsis non-survivor (n=39)		Statistical analysis	
	Mean	SD	Mean	SD	t-test	p-value
PCT	10.9518	13.99435	13.6297	15.88192	2.019	0.022*
IL-6	61.9967	41.25637	86.3821	38.81848	1.819	0.003*
TNF-α	16.0757	3.08095	16.5400	3.43995	1.667	1.009
LACTATE	4.5197	1.63314	5.0344	1.49421	0.699	0.990
S.FERRITIN	1161.9492	1228.87189	1393.8410	1637.90697	1.438	0.011*

Table 4: Mean value of SOFA score at day 7 and correlation of score with mortality

SCORE	Sepsis survivor (n=61)		Sepsis non-survivor (n=39)		Statistical analysis	
	Mean	SD	Mean	SD	t-test	p-value
SOFA SCORE	3.8852	1.05037	9.0256	1.18070	2.560	0.045*

***p-value<0.05 is significant**

Table 5: Mean value of biomarkers at day 7 and correlation of biomarkers with mortality

Biomarkers	Sepsis survivor (n=61)		Sepsis non-survivor (n=39)		Statistical analysis	
	Mean	SD	Mean	SD	t-test	p-value
PCT	2.4344	2.08701	37.1897	13.47137	2.881	0.022*
IL-6	17.1049	6.45865	110.6282	13.20799	1.718	0.019*
TNF-□	11.4279	2.84131	17.0769	3.58641	1.110	0.037*
LACTATE	3.1951	1.33409	6.5385	3.48415	1.615	0.001*
S. FERRITIN	370.7016	241.38026	1111.8462	956.12558	0.718	0.007*

***p-value<0.05 is significant**

Table 6: Mean value of biomarkers and score on days 1 and 7 in both groups

Biomarkers	Sepsis survivor (n=61)		Sepsis non-survivor (n=39)	
	Day 1	Day 7	Day 1	Day 7
PCT	10.9518±13.9	2.4344±2.08	13.6297±15.88	37.1897±13.4
IL-6	61.9967±41.2	17.1049±6.45	86.3821±38.8	110.6282±13.2
TNF-α	16.0757±3.08	11.4279±2.8	16.5400±3.4	17.0769±3.5
LACTATE	4.5197±1.63	3.1951±1.3	5.0344±1.49	6.5385±3.48
S. FERRITIN	1161.9492±1228.8	370.7016±241.4	1393.8410±1637.9	1111.8462±956.13
SOFA SCORE	6.26±1.55	3.8852±1.05	6.359±1.51	9.0256±1.18

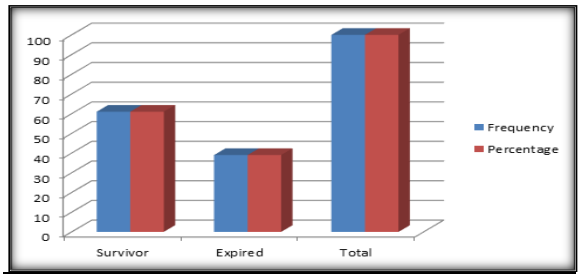

Figure 1: Showing the Distribution of patients according to mortality

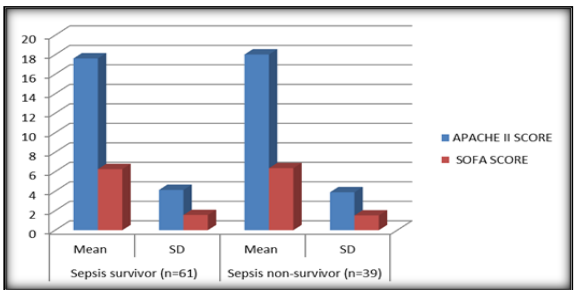

Figure 2: Mean value of score at day 1 and correlation of score with mortality

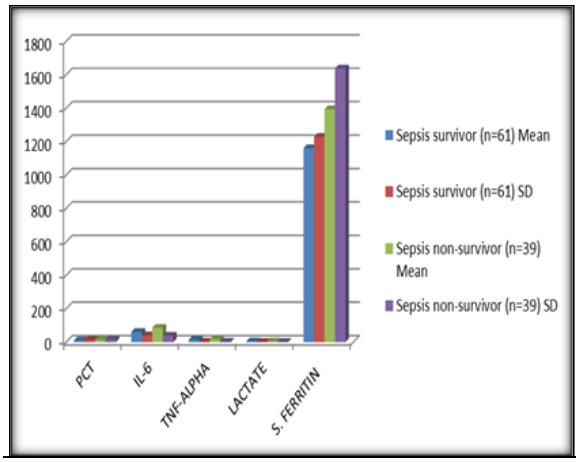

Figure 3: Showing Mean value of biomarkers at day 1 and correlation of biomarkers with mortality

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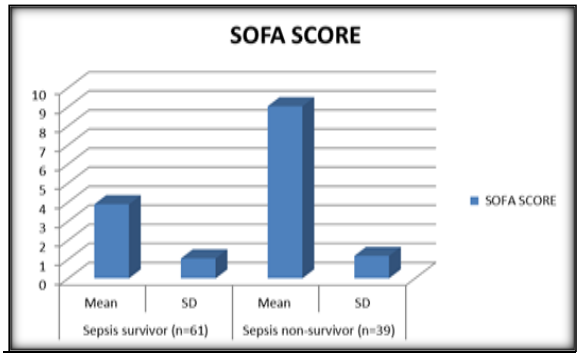


Figure 4: Showing Mean value of score at day 7 and correlation of score with mortality

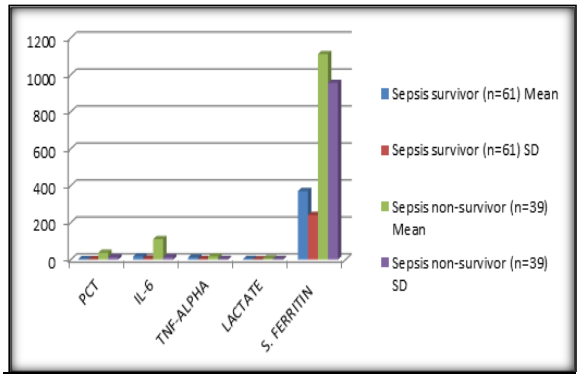


Figure 5: Mean value of biomarkers at day 7 and correlation of biomarkers with mortality

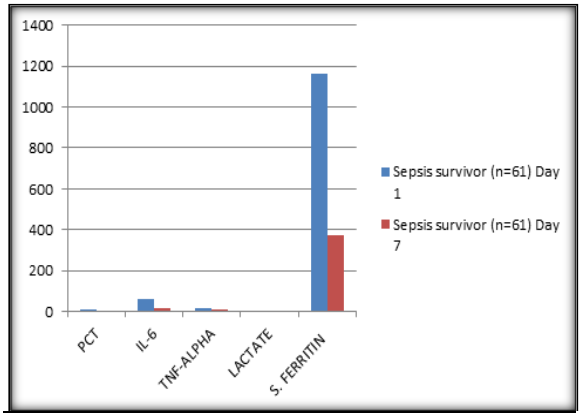


Figure 6: Mean value of biomarkers and score on day 1 and 7 in survivor groups

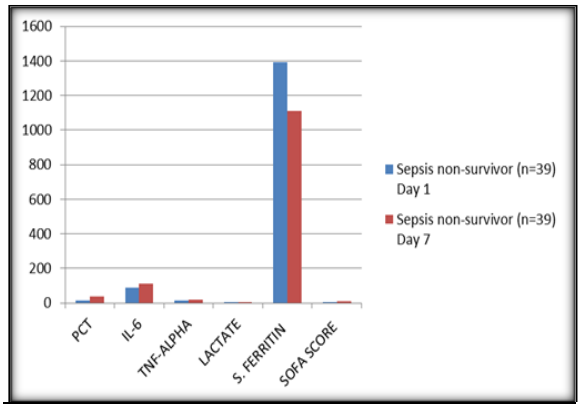
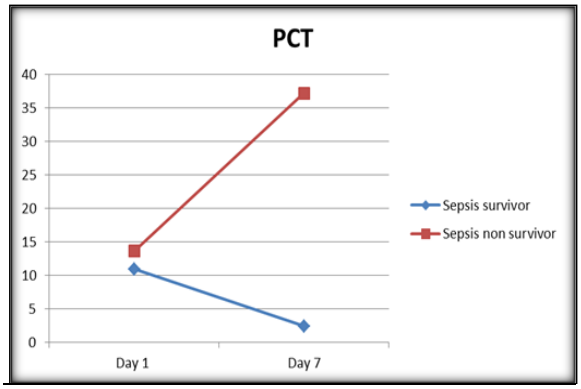
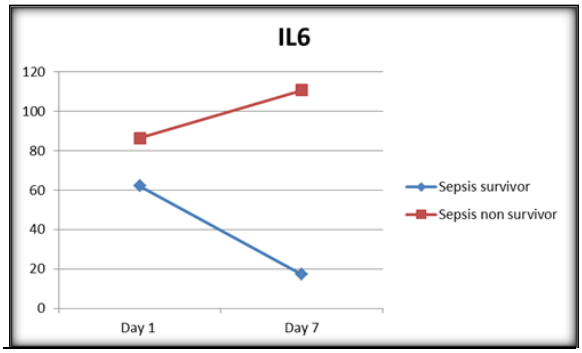


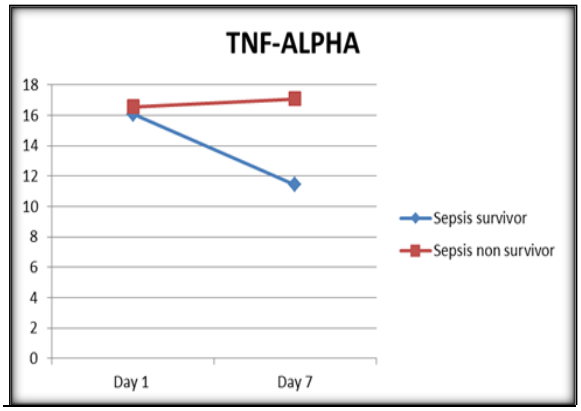
Figure 7: Mean value of biomarkers and score at days 1 and 7 in non-survivor groups



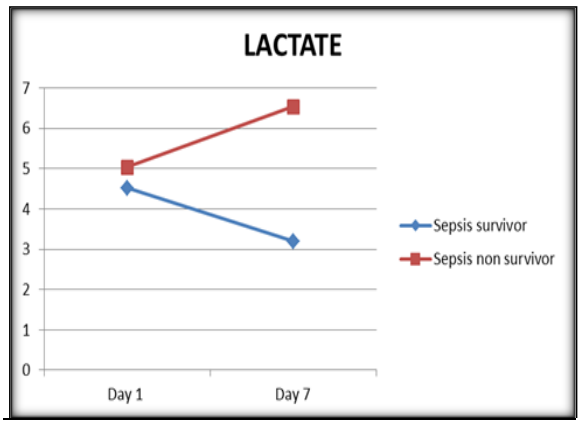
Line diagram 1: shows PCT value on day 1 and day 7 in both survivors and non-survivors groups.



Line diagram 2: shows the IL-6 value on day 1 and day 7 in both survivors and non-survivors groups



Line diagram 3: shows TNF-α value on day 1 and day 7 in both survivors and non-survivors groups



Line diagram 4: shows Lactate value on day 1 and day 7 in both survivors and non-survivors groups

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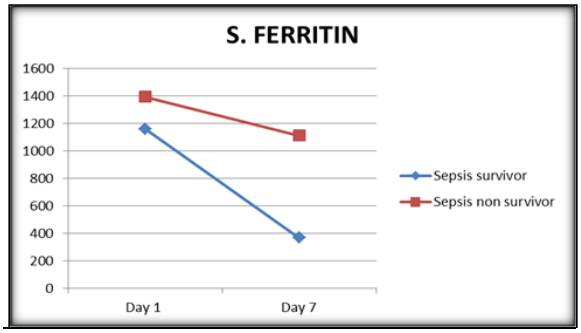
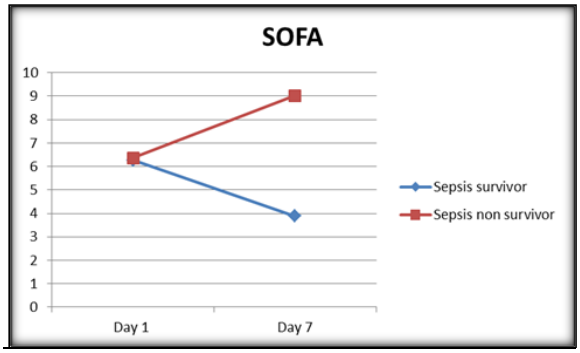


Line diagram 5: shows S. Ferritin value on day 1 and day 7 in both survivors and non-survivors groups



Line diagram 6: shows SOFA Score value on day 1 and day 7 in both survivors and non-survivors groups

DISCUSSION

Severe sepsis and septic shock are the most common causes of morbidity and mortality in critically ill patients. Different markers are used to predict sepsis. These markers are usually acute-phase reactants that increased during inflammation. Some of them are Cellular count, CRP, PCT, IL6, TNF-α, Ferritin, and Lactate. However, despite dramatic improvements in our knowledge of the pathogenesis, diagnosis, and therapeutic and supportive care, the mortality of septic patients remains unacceptably high with the overall rate in the range of 20.0-50.0 % in severe sepsis cases and increasing to 40.0-80.0 % in septic shock patients.[17] So need of the hour is to act fast and have reliable biomarkers and scoring systems that may help in proceeding and managing patients in the right direction. Biomarkers have great potential to improve the diagnosis and treatment of sepsis. The future of sepsis biomarkers lies in extensive validation studies of such novel biomarkers across heterogeneous populations and exploration of their power in combination.

The study consisted of 100 patients admitted to tertiary level ICU with the suspicion of sepsis or septic shock and out of 100 patients, 61 patients survived with a mean ICU stay of 13.01±2.28 days while 39 patients expired with a mean stay of 13.17±4.27. Showing mortality in sepsis is around 39 % which is consistent with Aggarwal R et al.[18]

On day 1, the APACHE II score is 17.6230 ± 4.12 and 18.0256 ± 3.88, SOFA score is 6.26 ± 1.55 in survivors and 6.35 ± 1.512 in non-survivor. While biomarkers PCT- 10.95 ± 13.99 and 13.62 ±15.88, IL-6–61.99 ± 41.25 and 86.38 ±38.81, TNF-α - 16.07±3.08 and16.54 ±3.43, LACTATE- 4.51 ±1.63 and 5.03 ±1.49, S. Ferritin 1161.94 ± 1228 and 1637 ± 1637 in survivor and non-survivor respectively. The single value of either the scoring system or biomarker is usually insignificant but has prognosticative value. In terms of mortality predictor PCT, IL-6, and S. ferritin shows more significant variability among the diseased and survivors.

At day 7, SOFA Score was 3.88 ± 1.05 and 9.025 ± 1.18 while PCT-2.43 ± 2.08 and 37.18 ± 13.47, IL-6- 17.10 ± 6.45 and 110.62 ± 13.20, TNF-α 11.42 ± 2.84 and 17.07 ± 3.58, LACTATE- 3.19 ± 1.33 and 6.53 ± 3.48 and S. FERRITIN - 370.70 ± 241 and 1111.84 ± 956 in survivor and non-survivor.

On day 1, PCT, IL-6, and S. Ferritin have statistically significant values whereas APACHE II score, SOFA score, lactate and TNF-α have statistically insignificant values. On day 7, all biomarkers as well as scoring systems have statistically significant values. When serial values are taken into account, serial biomarkers values are more significant than scoring systems and among the biomarkers, statistically significant results are shown with IL-6 followed by serum ferritin followed by PCT, lactate, and TNF-α. On day 7, we observed the values of biomarkers significantly associated with SOFA scoring which can facilitate our diagnosis of sepsis and septic shock along with its progression and risk stratification.

Our findings were comparable to the study performed by Lorenz and Daniel who reported that IL-6 is better than PCT and CRP in predicting the treatment success of non-surgical sepsis within the first 48-72 hours.

Jekarl et al. reported in their study that survivors of sepsis showed a rapid IL-6 reduction, while non-survivors showed persistently high IL-6 concentration (19). Due to the fast induction of IL-6 and very short half-life, it seems to be better than PCT and CRP in displaying the extent of inflammation and treatment success.[20]

Juhyun Song reported in his study that IL-6 levels in the initial blood samples obtained from patients with septic shock significantly decreased in the recovery group but increased among the death group, which suggests that IL-6 levels can be used to monitor the effectiveness of treatment for septic shock.[21] One of the largest studies done by Reinhart et al comprising 944 septic patients revealed that the patients with IL-6 over 1000 pg/ml had a mortality of 56% compared to 40% of those below this IL-6 level.[22]

A significant positive association was seen between the early elevations of both PCT, IL-6 and infectious complications. Similarly, a delayed or absent 24-hour lactate clearance helped to identify patients at

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risk of infectious complications and subsequently prolonged ICU and hospital stays. Due to financial constraints and availability issues, PCT is preferred over IL-6.

In this study, we concluded that SOFA score could be a more accurate predictor of severity and prognosis than the APACHE II score for in-hospital death. The results of our study were also supported by the study of Juhyun song. Their study showed that the combined biomarker approach showed good performance in predicting mortality in sepsis and septic shock patients than the single biomarker. The prognostic value of this approach was superior to that of the SOFA score and could therefore be a supplement to the SOFA score for predicting mortality. So Serial biomarkers have better prognostic value than APACHE II and SOFA scores in patients with sepsis and septic shock.

CONCLUSION

Our study concluded that a combined approach of various biomarker shows good performance in predicting mortality in sepsis and septic shock patients than single biomarker. Also, this approach is superior to scoring system approach alone i.e. SOFA score.

When serial values are taken into account serial biomarkers values are more significant than scoring systems and among biomarkers, statistically significant results are shown with IL-6 followed by s. ferritin, PCT, lactate, and TNF-α.

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