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Original Article

Anaesthesia Section

Comparative Evaluation of Procalcitonin and Interleukin-6 as Diagnostic and Prognostic Biomarkers for Sepsis

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ABSTRACT

Introduction: Diagnosis of sepsis is based on host's systemic inflammatory response to infection including life-threatening organ dysfunction. Various biomarkers are available for diagnosis and prognostication of patients with sepsis, Procalcitonin (PCT) and interleukin-6 (IL-6) being most reliable.

Aim: To compare PCT and IL-6 as diagnostic and prognostic biomarkers of sepsis in patients admitted with Systemic Inflammatory Response Syndrome (SIRS).

Materials and Methods: After taking Ethical Committee Approval, a total of 51 patients aged 15-65 years admitted in ICU with SIRS were identified. Patients with baseline Sequential Organ Failure Assessment (SOFA) score of 0 and 1 were categorised into non-infectious group and SOFA of greater than 2 into infectious group. Procalcitonin and IL-6 were measured on day 1 and 3 using enzyme-linked immunosorbent assay. Collected data were analysed using SPSS software version 22.0. Parametric data were compared using Student's t-test. Other tests used were Mann-Whitney U test, Pearson's chi-square test, Fisher's-exact test, Friedman's test, ANOVA.

Results: PCT (day 1 and 3) was significantly higher in the infectious group than non-infectious group ($p<0.001$) and day 1 PCT was found to be better in diagnosing sepsis with Area Under the Curve (AUC) of 0.90 (95% CI, 0.789-1.000) ($p=0.001$). Unlike day 1 PCT, day 3 PCT was statistically significant in predicting mortality with AUC of 0.982 (95% CI, 0.956-1.000) ($p<0.005$). IL-6 was found to be better in predicting mortality with day 1 AUC of 0.987 (95% CI, 0.966-1.000) ($p<0.005$) and day 3 AUC of 0.981 (95%CI, 0.953-1.000) ($p<0.005$). Multivariate analysis of mortality prediction showed day 1 IL-6 to have a better mortality prediction value ($p=0.047$).

Conclusion: PCT on day 1 was found to be better in identifying sepsis and day 1 IL-6 and day 3 PCT in predicting mortality.

Keywords: Diagnostic biomarkers, Sepsis-3, Sequential organ failure assessment score, Systemic inflammatory response syndrome

INTRODUCTION

Sepsis is a life-threatening complication caused by an exaggerated immune response to infection. In 1991, the American College of Chest Physicians/Society of Critical Care Medicine (ACCS/SCCM) consensus conference had defined sepsis focusing on host's systemic inflammatory response to infection [1]. SIRS was defined as a patient having at least two of the following criteria: 1) Temperature >38°C or <36°C; 2) Heart rate >90/minute; 3) Respiratory rate >20/minute or $PaCO_2$ <32 mmHg; 4) White blood cell count >12000/mm^3 or <4000/mm^3 or >10% immature bands. A 2001 task force recognised limitations of these definitions but could not offer any alternative because of the lack of supporting evidence [2]. Later on in the year 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection in which organ dysfunction can be identified as an acute change in SOFA score of 2 points or more consequent to infection [3,4]. Meanwhile, septic shock was defined as a subset of sepsis with circulatory and metabolic abnormalities identified clinically with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg and having a serum lactate level >2 mmol/L despite adequate volume resuscitation.

Although the definite incidence is uncertain, there are conservative estimates that indicate sepsis is a leading cause of mortality and critical illness worldwide [5,6]. Early intervention in patients with sepsis can have a significant effect on survival rates and several researches have been undertaken to identify factors in the blood that could signal sepsis before it becomes severe. This leads to the advent of biomarkers in early diagnosis and management of sepsis. Although, a lot of biomarkers like interleukin (IL)-1b, IL-6, IL-8, IL-10, PCT, C-reactive protein are available for investigating sepsis, PCT and IL-6 have been shown to be more reliable in diagnosis and risk stratification of sepsis [7-11]. However, the sensitivity and specificity of both PCT and IL-6 show marked variation in relation to the severity of infection and cut-off values [12,13]. Moreover, some earlier studies have produced conflicting results regarding these biomarkers [14].

This prospective observational study was undertaken with the purpose of evaluating the role of PCT and IL-6 in early diagnosis of sepsis in patients admitted in the intensive care unit and predicting their survival.

MATERIALS AND METHODS

This prospective observational study was conducted after getting approval from the hospital Ethical Committee (520/Ethics/R.Cell-17) and written informed consent from the patients/relatives. A total of 51 patients aged 15 to 65 years admitted to the intensive care unit between September 2016 to August 2017 and fulfilling SIRS criteria were included in the study. Patients with already known organ dysfunction and those transferred from other intensive care units were excluded from the study.

Patients admitted with SIRS were assessed clinically by the intensive care doctor present at the time of admission. Baseline clinical parameters like temperature, heart rate, respiratory rate,

blood pressure, white cell count were recorded. Patients were also assessed for any clinical signs of infection. Acute Physiology And Chronic Health Evaluation (APACHE) II score and SOFA score were measured at the time of admission. Blood, urine and sputum cultures were sent accordingly before starting antibiotics. Patients were divided into the infectious and non-infectious group based on clinical assessment and baseline SOFA scores. Patients with baseline SOFA score of 0 and 1 were considered as the non-infectious group and SOFA score of 2 or more was considered as the infectious group.

SOFA values were measured every day and biomarkers (PCT and IL-6) were measured from the patient's serum on day 1 and day 3 of admission. The blood samples taken for estimation of biomarkers (PCT and IL-6) were centrifuged and stored at -80°C and were analysed using Enzyme-Linked Immunosorbent Assay Technique (ELISA).

Sample size was calculated using the formula:

$$n=(z_{1-\alpha/2})^2 * P*(100-P)/d^2$$

where n=sample size; Z=value of two-tailed alpha error; P=expected prevalence; d=allowable error. Value of Z statistic for the level of significance 0.05 is 1.96. According to Mat-Nor MB et al., 69% of SIRS patients had infective pathology; so P=69%; d=20% of prevalence=13.8 [15]. From the above mentioned formula, sample size was calculated as 43 and taking 20% dropout rate, sample size of 51 was taken for the present study.

STATISTICAL ANALYSIS

Data were expressed as mean±SD for continuous parametric data otherwise median with interquartile range were used. A p-value <0.05 was considered significant. Data collected were analysed statistically using SPSS software version 22.0 Chicago, USA. Continuous data were compared using Student's t-test if data were parametric; otherwise appropriate non-parametric test was used. Other tests used were: Mann-Whitney U test, Pearson's chi-square test, Fisher's-exact test, Friedman's test, ANOVA.

RESULTS

The age of patients ranged from 17 to 61 years with an average of 38.2±13.1 years. Overall, there were 30 female patients (58.8%) and 21 males (41.2%), however, the difference was statistically insignificant (χ^2=4.4, p=0.20) [Table/Fig-1]. Average age of males and females were also comparable (43.7±14.1 vs. 34.4±11.2; p=0.06) [Table/Fig-1].

Variables	Male	Female	Total	χ^2	p-value
Number (%)	21 (41.2%)	30 (58.8%)	51 (100%)	4.4	0.20*
Age in years (Mean±SD)	43.7±14.1	34.4±11.2	38.2±13.1	-	0.06†

[Table/Fig-1]: Overall age and sex distribution of the study population.
*Non-parametric chi-square test used; †Independent t-test used; p-value <0.05 is significant

Out of total 51 patients, 35 patients (69%) were enrolled in the infectious group based on the clinical assessment and baseline SOFA score of ≥2 and 16 patients (31%) were enrolled in the non-infectious group (SOFA score 0 and 1). Majority of study population belonged to the infectious group and this difference was found to be statistically significant (p<0.05). There was no significant difference in baseline parameters between the two groups except for APACHE score which was significantly higher in the infectious group (p<0.001) [Table/Fig-2]. Length of mechanical ventilation in days, duration of ICU stay in days and blood culture positivity was found to be more in the infectious group [Table/Fig-3].

PCT was found to be significantly higher in the infectious group on both day 1 and 3 with a mean of 1477.8±364.7 pg/mL on day 1 (p<0.001) and mean of 1153.4±611.8 pg/mL on day 3 (p<0.001) [Table/Fig-4]. IL-6 was also found to be significantly higher in the infectious group on both days with a mean of 260.2±104.9 pg/mL on day1 (p<0.001) and mean of 138.0±53 pg/mL on day 3 (p<0.003) [Table/Fig-4].

Variables	Infectious (n=35)	Non-infectious (n=16)	p-value*
	Mean±SD	Mean±SD	
Heart rate (beats per minute)	120.7±20.3	109.8±24.5	0.1
Respiratory rate (breaths per minute)	19.8±5.9	20.5±4.6	0.67
Temperature (Fahrenheit)	99.7±0.7	99.3±0.8	0.05
TLC (counts per cubic mm)	15824.3±6864.1	15754.4±13887.7	0.98
APACHE-II†	20 (16.0-25.0)	12 (9.3-14.8)	<0.001

[Table/Fig-2]: Distribution of baseline parameters.
*Independent t-test used; †Median and interquartile range are calculated, Mann Whitney U test used; p-value <0.05 is significant

Continuous variables	Infectious (n=35)	Non-infectious (n=16)	p-value*
	Mean±SD	Mean±SD	
Duration of MV (days)	6±5.2	3.3±4.6	0.07
Length of ICU stay (days)	8.3±5.5	5.6±3.9	0.03
Categorical variables	**Infectious (n=35)**	**Non-infectious (n=16)**	**p-value†**
	No (%)	No (%)	
Blood culture positivity	11 (31.4)	2 (12.5)	0.15
Blood culture negativity	24 (68.6)	14 (87.5)	
Survivors	19 (54.3)	12 (75)	0.048
Non-survivors	16 (45.7)	4 (25)	

[Table/Fig-3]: Relationship of outcomes among groups.
*Independent t-test used; †Pearson's chi-square test used; p-value <0.05 is significant

Biomarkers	Infectious	p-value*	Non-infectious	p-value*	p-value†
	Mean±SD		Mean±SD		
Procalcitonin (pg/mL)					
Day 1	1477.8±364.7	0.04	730.9±411.8	0.046	<0.001
Day 3	1153.4±611.8		528.7±458.4		<0.001
Interleukin-6 (pg/mL)					
Day 1	260.2±104.9	<0.001	162.2±61.7	<0.001	<0.001
Day 3	138.0±53.0		99.2±32.6		<0.003

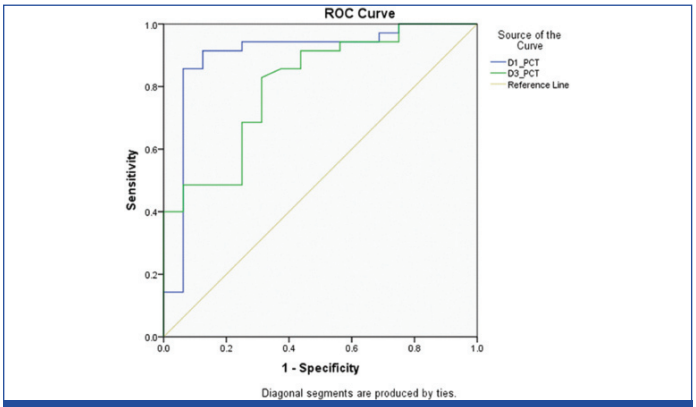
[Table/Fig-4]: Distribution of biomarkers among infectious and non-infectious groups.
*Paired t-test used; †Independent t-test used; ‡One-way repeated measures ANOVA with Greenhouse Geisser correction used; p-value <0.05 is significant

The levels of biomarkers among survivors and non-survivors group are presented in [Table/Fig-5]. PCT levels were significantly reduced on day 3 among survivors (527.5±340.5 pg/mL) when compared with day 1 levels (1115.8±578.8 pg/mL) (p<0.001), however among non survivors the levels of PCT increased on day 3 (1623.7±330.7 pg/mL) when compared with day 1 (1442.2±311.7 pg/mL), though it was statistically insignificant (p=0.05). However, IL-6 levels were significantly reduced on day 3 when compared with day 1 both in the survivors (94.1±18.0 vs. 164.2±47.3) (p<0.001) as well as in the non-survivors (175.3±44.8 vs. 330.6±83.8) (p<0.001). IL-6 levels were found to be significantly higher among non-survivors on day 1 (330.6±83.8 pg/mL) (p<0.001) as well as on day 3 (175.3±44.8 pg/mL) (p<0.001) in comparison with survivors in the present study [Table/Fig-5].

Biomarkers	Survivors	p-value*	Non-survivors	p-value*	p-value†
	Mean±SD		Mean±SD		
Procalcitonin (pg/mL)					
Day 1	1115.8±578.8	<0.001	1442.2±311.7	0.05	<0.001
Day 3	527.5±340.5		1623.7±330.7		<0.001
Interleukin-6 (pg/mL)					
Day 1	164.2±47.3	<0.001	330.6±83.8	<0.001	<0.001
Day 3	94.1±18.0		175.3±44.8		<0.001

[Table/Fig-5]: Distribution of bio markers among survivors and non survivors.
*Paired t-test used; †Independent t-test used; ‡One-way repeated measures ANOVA with Greenhouse Geisser correction used; p-value <0.05 is significant

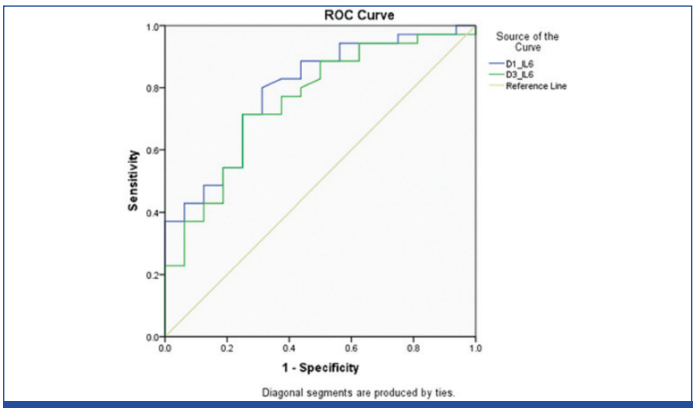
The diagnostic value of PCT in the evaluation of patients with sepsis has been summarised in [Table/Fig-6,7] and that of IL-6 in [Table/Fig-8,9]. From this Receiver Operating Characteristic (ROC) curve, it is clear that PCT had better diagnostic value than IL-6 in the evaluation of sepsis. Day 1 PCT level was found to be better in diagnosing infection in comparison to day 3 levels with AUC of 0.90±0.057 (95% CI, 0.789-1.000) (p<0.001). At a cut-off value of 1006.7 pg/mL Day 1 PCT was found to be 88.6% sensitive and 87.5% specific in diagnosing sepsis.



[Table/Fig-6]: ROC Curve for Day 1 and 3 Procalcitonin comparison.

Area under the curve					
Test result variables	Area	Std. Error*	Asymptotic Sig.†	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Day 1 PCT	0.900	0.057	<0.001	0.789	1.000
Day 3 PCT	0.806	0.065	<0.001	0.679	0.933

[Table/Fig-7]: Day 1 and 3 Procalcitonin comparison for diagnosing sepsis.
The test result variable(s): Day 3 PCT has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
*Under the nonparametric assumption; †Null hypothesis: true area=0.5

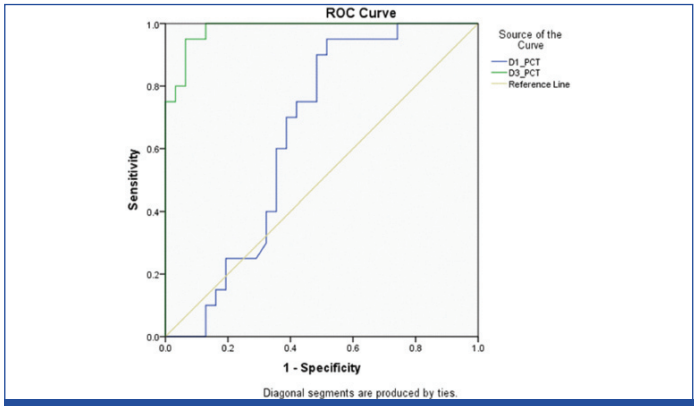


[Table/Fig-8]: ROC Curve for Day 1 and 3 Interleukin-6 comparison.

Area under the curve					
Test result variables	Area	Std. Error*	Asymptotic Sig.†	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Day 1 IL6	0.794	0.066	<0.05	0.664	0.923
Day 3 IL6	0.756	0.072	<0.001	0.615	0.898

[Table/Fig-9]: Day 1 and 3 interleukin-6 comparison for diagnosing sepsis.
The test result variables: Day 1 IL6, Day 3 IL6 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
*Under the nonparametric assumption; †Null hypothesis: true area=0.5

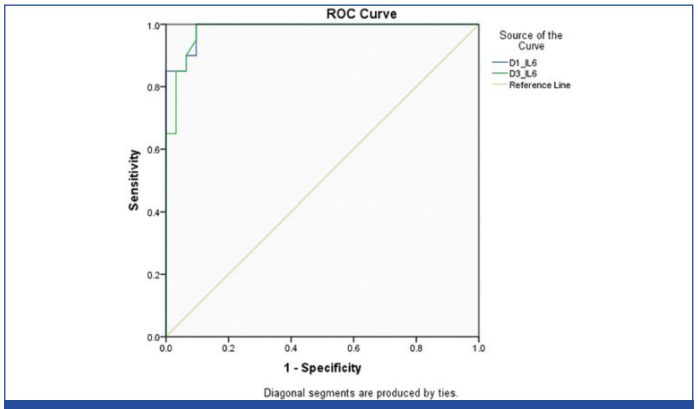
The ability of PCT in predicting the mortality has been summarised in [Table/Fig-10,11] and that of IL-6 in [Table/Fig-12,13]. PCT levels measured on day 1 was found to be statistically insignificant in predicting mortality (p=0.081) whereas day 3 levels were found to be statistically significant in predicting mortality with AUC of 0.982±0.014 (95%CI, 0.956-1.000) (p<0.005). Similarly, from the above ROC curve it is clear that both day 1 and 3 IL-6 levels were better in predicting the mortality with day 1 AUC of 0.987±0.011 (95% CI, 0.966-1.000) (p<0.005), and day 3 AUC of 0.981±0.014 (95%CI, 0.953-1.000) (p<0.005). The multivariate analysis of mortality prediction shows that day 1 IL-6 has a better mortality prediction value of 1.215 (95% CI, 1.002-1.447) (p=0.047) [Table/Fig-14].



[Table/Fig-10]: ROC curve for Day 1 and 3 procalcitonin for mortality prediction.

Area under the curve					
Test result variables	Area	Std. Error*	Asymptotic Sig.†	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Day 1 PCT	0.646	0.077	0.081	0.494	0.797
Day 3 PCT	0.982	0.014	<0.005	0.956	1.000

[Table/Fig-11]: Day 1 and 3 Procalcitonin comparison for mortality prediction.
The test result variables: Day 1 PCT has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
*Under the nonparametric assumption; †Null hypothesis: true area=0.5



[Table/Fig-12]: ROC Curve for Day 1 and 3 Interleukin-6 for mortality prediction.

Area under the curve					
Test result variables	Area	Std. Error*	Asymptotic Sig.†	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Day 1 IL6	0.987	0.011	<0.005	0.966	1.000
Day 3 IL6	0.981	0.014	<0.005	0.953	1.000

[Table/Fig-13]: Day 1 and 3 Interleukin-6 comparison for mortality prediction.
The test result variables: Day 1 PCT, Day 3 IL6 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
*Under the nonparametric assumption; †Null hypothesis: true area=0.5

	Exp (B)	95% CI for EXP (B)		p-value
		Lower	Upper	
Day 1 IL6	1.215	1.002	1.447	0.047
Day 3 IL6	1.080	0.849	1.587	0.393
Day 1 SOFA	3.024	0.561	16.824	0.261
Day 3 SOFA	1.724	0.832	4.338	0.532

[Table/Fig-14]: Multivariate analysis in predicting mortality.
Adjusted for age, sex and PCT; p-value significant at <0.05

DISCUSSION

Early diagnosis and intervention play a pivotal role in the management of sepsis, failing which there can be significant fatality [16,17]. The major impediment in diagnosing sepsis is because of the lack of sensitivity and specificity of routine laboratory tests and the fact that confirmatory microbiologic tests are not instantly available. This paved the way for the search of an ideal marker in identifying patients with sepsis and predicting their survival. Though there are many biomarkers available for investigating sepsis, PCT and IL-6 have been shown to be more reliable in diagnosing sepsis as well as in predicting mortality from sepsis.

PCT is a precursor of calcitonin, produced in thyroidal and adipose tissue in healthy individuals. The normal serum value of PCT is <0.1 ng/mL. Assicot M et al., first reported the presence of increased levels of PCT in systemic infections [18]. Simon L et al., in their study found PCT to be remarkable in differentiating bacterial from the non-infectious causes of inflammation [19].

IL-6 is a cytokine secreted by activated monocytes and macrophages. The normal serum concentration of IL-6 is <5 pg/mL with a plasma half-life of less than six hours. A study reported that plasma levels of IL-6 were found to be elevated earlier than C-reactive protein and may be used as a diagnostic marker for sepsis [20]. Besides, being used as a diagnostic test for the presence of sepsis, it is also used as a prognostic factor for predicting outcome in such patients [21].

In a previous study done by Mat-Nor MB et al., evaluating the efficacy of PCT and IL-6 in diagnosing sepsis they categorised patients into the infectious and non-infectious groups based upon a clinical assessment by the admitting physician [15]. However, in the present study, authors also included baseline SOFA score along with clinical evaluation for categorising the patients, in accordance with the latest "Sepsis-3" guidelines [3]. "Sepsis-3" has removed SIRS in defining sepsis and has described sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection in which organ dysfunction can be identified as an acute change in SOFA score of two points. Therefore, patients with baseline SOFA score of 0 and 1 were enrolled in the non-infectious group and SOFA score of 2 or more were enrolled in infectious group in the present study. Applying the above categorisation, we found that in the present study, a significantly higher number of patients 69% (n=35) belonged to infectious group and only 31% (n=16) belonged to non-infectious group, which shows a very high prevalence of sepsis in patients admitted in intensive care unit. This finding was very similar to that of Mat-Nor MB et al., who found infective pathology in 69% of patients [15].

The present study demonstrated that PCT concentrations on the day of admission and on day 3 could differentiate sepsis from non-infectious SIRS. They were more accurate than IL-6 in diagnosing sepsis with maximum AUC of 0.900 (95% CI, 0.789-1.000) on day 1 and area under the curve of 0.806 (95%CI, 0.679-0.933) on day 3.

Nargis W et al., evaluated the utility of PCT as a routine biochemical tool in which they measured serum concentration of PCT in 73 intensive care patients and found that PCT had a higher sensitivity (76%) and specificity (72%) in the diagnosis of sepsis [22]. Chengfen Y et al., in a meta-analysis concluded that PCT can be used as a good auxiliary biomarker and demonstrated that the pooled sensitivity was 74% (95% CI, 72%-76%), the pooled specificity was 70% (95% CI,67%-72%) and the pooled AUC was 0.83 (95% CI, 0.79-0.87) [23]. A comparison between PCT and IL-6 was done by Harbarth S et al., in which PCT yielded the highest discriminative value, with AUC of 0.92 (CI, 0.85-1.0), followed by IL-6 with AUC of 0.75 (95% CI, 0.63-0.87) [24]. The current study showed that day 1 PCT was diagnostic of sepsis and this finding was similar to the study done by Harbarth S et al., [24]. The accuracy for diagnosing sepsis with IL-6 is less because it is an acute phase inflammatory cytokine wherein the level rises in two hours and gradually declines to undetectable levels within approximately 24 hours [25,26]. This early phase of infection could have been missed in the present study as patients progressed to severe form on ICU arrival.

Early risk stratification and intervention should be done once the diagnosis is established. Biomarkers can help in predicting mortality and organ dysfunction. In the present study, we found that levels of both PCT and IL-6 were higher among non-survivors in comparison with survivors. IL-6 levels on both day 1 and 3 was found to be higher among non survivors and the AUC for day 1 was 0.987 (95% CI, 0.966-1.000) and for day 3 was 0.981 (95% CI, 0.953-1.000), whereas PCT showed a maximum AUC of 0.982 (95% CI, 0.956-1.000) on day 3.

Liu D et al., in a systematic review and meta-analysis, concluded that elevated PCT levels and non-clearance of PCT had a higher risk of death and therefore initial PCT level is of limited prognostic value in sepsis patients [27]. The current study showed similar results of persistently elevated PCT levels among non-survivors and a significant fall in PCT among survivors.

Authors had also done a multivariate regression analysis for mortality prediction which showed IL-6 on day 1 was more predictive of mortality than day 3. Besides, the duration of ICU stay was also found to be significantly higher in infectious group in comparison with non-infectious group. Summarising from the biomarker evaluation, it was found from the present study that day 1 PCT was better in diagnosing sepsis whereas, day 3 PCT and day 1 IL-6 were better in predicting mortality of patients admitted with sepsis.

LIMITATION

This was a single centre study over a short span of time with relatively less number of patients. Larger multi-centre studies over longer periods with customisation for the Indian ICU population are needed. Most of the patients in the present study were postoperative patients which may not be reflective of the true patient population of an average ICU and may have some influence on the overall results of the study. Also, authors have not analysed the lead time of the patients to ICU admission, which is an important factor that can affect overall prognosis and patient survival. Moreover, since this was an observational study and biomarkers were analysed later, no intervention was done on the patient and therefore, there was no significant change in patient outcome.

CONCLUSION

We conclude that serum PCT concentrations measured at the time of admission (within 24 hours of admission in ICU) can help in differentiating sepsis from non-infectious SIRS. This can guide the intensivist in planning appropriate intervention to reduce mortality and avoid unnecessary diagnostic tests. Similarly, day 3 PCT and day 1 IL-6 demonstrated better efficacy in predicting mortality and risk stratification of patients with sepsis. In view of the complexities of the host response to infection and the diversity of organisms, no single sepsis biomarker seems to be ideal in diagnosing sepsis or in predicting mortality. Hence, future studies should be directed at evaluating the efficacy of the combination of biomarkers (multi-marker approach) along with clinical indices in managing sepsis.

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