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ROLE OF CHEAPER COMBINED BIOMARKERS LIKE WHITE CELL COUNT, EOSINOPHIL COUNT, PLATELET COUNT AND CRP TOGETHER IN PREDICTING 14 DAY MORTALITY OF ICU PATIENTS WITH SEPSIS

Medicine

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ABSTRACT

Background and Objectives: Sepsis is a common cause of mortality and morbidity especially in resource poor settings in India.[1] It is the need of the hour to devise efficient and cheaper biomarkers to diagnose and predict prognosis in sepsis, so that appropriate antibiotic therapy can be initiated. We conducted the study to find out the predictability of 14 day mortality in patients with sepsis by combined biomarkers and also to compare the diagnostic validity of the combined biomarkers with individual biomarkers. **Methodology:** We enrolled eighty six patients (forty three consecutive cases with sepsis and an equal number of age and sex matched controls without sepsis).Convenient sampling was done. Study period was for two months. All patients were followed up for a period of 14 days to assess mortality. Clinical and biochemical parameters were analysed. **Results:** Fourteen day mortality rate observed was 41.9% (18/43). Area under curve obtained in ROC curves suggested combined bioscore as a significant predictor of mortality (0.724 ± 0.081). Combined bioscore of ≥ 3 had sensitivity of 77.8 % and specificity of 56 % in predicting mortality. Combination of white cell count, absolute eosinophil count and platelet count was found to be the best predictor [sensitivity of 38.8 %, specificity of 96 %, PPV of 87.5 %, NPV of 68.6 % , (p = 0.006)]. In multivariate logistic regression, combined bioscore was found to be an independent predictor of sepsis with a very significant Odds Ratio of 10.661 (95 % CI, 2.179 – 52.165). **Conclusion:** The biomarkers which we had analysed in combination could serve as a valuable predictor of 14 day mortality in sepsis. By selecting the right antibiotic based on severity of sepsis, development of antimicrobial resistance and thus health care cost can be reduced.

KEYWORDS

sepsis, biomarkers, prognosis, mortality

INTRODUCTION:

Sepsis is defined as a dysregulated host response to infection, leading on to life threatening organ dysfunction. India has one of the highest infectious disease burden in the world. [1] Delay in diagnosis and initiation of appropriate antimicrobials are the most important reasons for mortality. [1,2]

If we can find out a single or combination of cheap parameters in patients with sepsis which can predict mortality, we will be able to initiate appropriate antimicrobials at the earliest and thus reduce mortality and emergence of antimicrobial resistance.

Biomarkers can help in this context. Different biomarkers, both conventional and newer were evaluated in diagnosing sepsis and predicting mortality. White cell count(total leucocyte count / TLC), platelet count , C- reactive protein (CRP), absolute eosinophil count (AEC) [3,4,5] and newer biomarkers like procalcitonin [6,7,8] were studied with varying success.

For physicians working in India with limited resources, it is of utmost importance to identify cost effective biomarkers which can predict mortality. Some studies showed that combination of biomarkers would be more useful for risk stratification in sepsis. [4]

In view of the paramount importance of early and accurate antimicrobial treatment in sepsis, we undertook the present study to find out whether combination of cheaper biomarkers like TLC, AEC, platelet count and CRP, can predict 14 day mortality in patients with sepsis.

Moreover on searching literature, to our knowledge there are no previous studies, which have assessed the combined efficacy of the above mentioned biomarkers in predicting prognosis of patients with sepsis.

OBJECTIVES:

1. To find out the predictability of 14 day mortality in patients with sepsis by combined biomarkers
2. To compare the diagnostic validity of the combined biomarkers with individual biomarkers.

MATERIALS AND METHODS:

This prospective cohort study was conducted from May 2019 to June 2019 in Intensive care unit (ICU). All patients with sepsis and an equal number of age and gender matched patients without sepsis were included in the study. They were followed up for 14 days to assess mortality. Convenient sampling technique was used.

Patients with age more than 18 years with infection and with q SOFA [quick SOFA (Sequential Organ Failure Assessment)] score of ≥2, were considered. Patients with post surgical sepsis or immunosuppressed, were excluded from the study.

The study was started upon approval from Institutional Ethics Committee and after getting informed consent. Detailed history taking and clinical examination were done. Patient's quick SOFA score was calculated. . Mortality was assessed at 14 days. Data was entered in Microsoft excel sheet .

Statistical analysis was done with IBM SPSS version 25. Mean, Standard deviation, Independent two sample t test / Mann-Whitney U test, Chi square test were used for analysis. ROC curve was applied to find out the cut off value of combined bioscore for predicting 14 day mortality and to check its validity. Multivariate logistic regression method was used to identify the independent factors which could predict mortality.

RESULTS:

We enrolled 86 patients (43 consecutive patients with sepsis and 43 age and gender matched patients without sepsis,as controls) admitted in ICU . Study period was for two months . All patients were followed up for a period of 14 days to assess mortality.

Baseline demographic characteristics of cases and controls is depicted in Table 1.

Table 1: Baseline Demographic Characteristics Of Cases And Controls

Characteristics	Cases (n=43)		Controls (n=43)		P value
Age	Mean	SD	Mean	SD	0.904
	57.58	17.05	57.14	16.87	

Gender	Males	Females	Males	Females	1.00
	28(65.11 %)	15(34.88 %)	28(65.11 %)	15(34.88 %)	
Comorbidities	Yes	No	Yes	No	0.662
	24(55.8%)	19(44.2%)	26(60.5)	17(39.5%)	
Hepatic dysfunction	15 (34.9%)		7 (16.3%)		0.048
Renal dysfunction	27 (62.8%)		6 (14%)		<0.001
Cardiac dysfunction	4 (9.3%)		4 (9.3%)		1.000
Pulmonary dysfunction	12 (27,9%)		8 (18.6%)		0.307

Biomarkers

When individual biomarkers were considered, we observed the following results (Table 2).

Table 2 : Characteristics Of Biomarkers Among Cases And Controls

Biomarkers	Groups	Total number of patients	Mean	SD	p Value
White cell count	Case	43	15793.49	6714.27	0.002
	Control	43	12083.72	7134.77	
Absolute eosinophil count	Case	43	86.03	215.78	0.056
	Control	43	143.78	262.26	
Platelet count	Case	43	260139.53	147273.41	0.836
	Control	43	257451.16	123081.51	
CRP	Case	43	16.54	8.50	< 0.001
	Control	43	4.69	2.54	

White cell count and CRP were found to be significant as independent predictors in diagnosing sepsis.

Receiver-operating Characteristic Curves (ROC curves)

When individual biomarkers (TLC, AEC, CRP, Platelet count) and combined bioscore (combining four biomarkers together) were plotted and analysed , the Area Under Curve (AUC) of the combined bioscore was found to be significantly higher than that of individual biomarkers.(Fig 1)

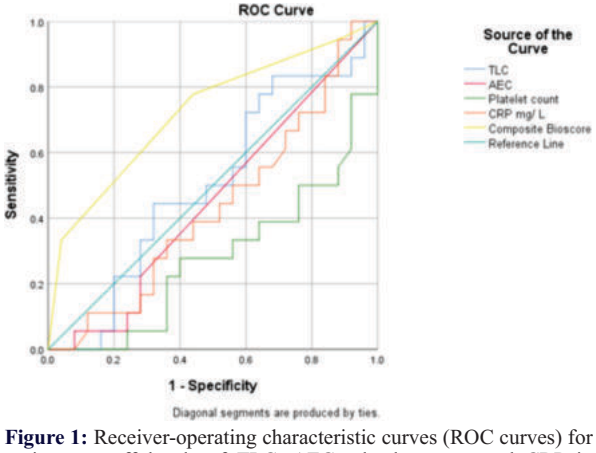

Figure 1: Receiver-operating characteristic curves (ROC curves) for various cut-off levels of TLC, AEC, platelet count and CRP in assessing the efficacy of combined bioscore compared to individual biomarkers in predicting mortality in patients with sepsis.

The AUC of combined bioscore was 0.724 ± 0.081, as compared to 0.502 ± 0.090 for TLC, 0.453 ± 0.089 for AEC, 0.433 ± 0.089 for CRP and 0.279 ± 0.079 for platelet count .The values obtained from area under the curve suggest combined bioscore as a significant predictor of mortality at 14 days, in patients with sepsis compared to individual biomarkers.

Cut off of 3.5 was obtained for combined bioscore according to receiver operating characteristic curve (ROC). Hence patients were stratified into two groups, one with combined bioscore of ≥ 3 and the other with bioscore of < 3. (Table 3)

Table 3 : Comparison Of Combined Bioscore Of Those With ≥ 3 And < 3 Between Cases And Controls

Combined Bioscore	Groups				p value
	Case		Control		
	n=43	%	n=43	%	
≥ 3	25	58.1	6	14.0	< 0.001
< 3	18	41.9	37	86.0	

This finding highlights that combined bioscore of ≥ 3 is a useful tool in assessing patients with sepsis.

Fourteen day mortality rate observed was 41.9% (18/43) among cases .Combined bioscore of ≥ 3 had a sensitivity of 77.8 %, specificity of 56 %, PPV of 56 % and an NPV of 77.78 % in predicting 14 day mortality in patients with sepsis. This observation denotes that combined bioscore of ≥ 3 would be able to predict 14 day mortality in patients with sepsis. (Table 4)

Table 4 : Comparison Of Combined Bioscore (≥ 3 vs < 3) Among Patients With Sepsis In Predicting 14 Day Mortality

Combined bioscore (n)	Mortality				p value
	Expired		Alive		
	n	%	n	%	
≥ 3 (25)	14	56.0	11	44.0	0.027
< 3 (18)	4	22.2	14	77.78	

Further analysis of combined biomarkers was done. We noticed the combination of TLC, AEC and platelet count as the best in predicting mortality, with a sensitivity of 38.8 %, specificity of 96 %, a positive predictive value (PPV) of 87.5 % and a negative predictive value (NPV) of 68.6 % , (p = 0.006). (Table 5) . Combination of all four biomarkers was found to have a sensitivity of 33.33 %, specificity of 96 %, PPV of 85.7 % and NPV of 66.7 % (p = 0.015) (Table6).

Table 5 : Significance Of Combined Bioscore (TAP)* In Predicting Mortality In Sepsis Patients

Combined bioscore (TAP)*	Groups				p value
	Case		Control		
	n=43	%	n=43	%	
Positive (8)	7	87.5	1	12.5	0.006
Negative (35)	11	31.4	24	68.6	

* TAP – Total Leucocyte count, Absolute eosinophil count, Platelet count

Table 6: Significance Of Combined Bioscore (TAPC)* In Predicting Mortality In Sepsis Patients

Combined Bioscore (TAPC)*	Groups				p value
	Case		Control		
	n=43	%	n=43	%	
Positive (7)	6	85.7	1	14.3	0.015
Negative (36)	12	33.3	24	66.7	

* TAPC – Total leucocyte count, Absolute eosinophil count, Platelet count, CRP

In multivariate logistic regression analysis of factors predicting mortality, combined bioscore was found to be an independent predictor of 14 day mortality in patients with sepsis with a very significant Odds Ratio (OR) of 10.661 (95 % CI, 2.179 – 52.165) (p = 0.003). (Table 7)

Table 7: Multivariate Logistic Regression Analysis Of Factors Predicting 14 Day Mortality In Sepsis Patients

Variables	coefficient	S.E.	p Value	Odds ratio (OR)	95% CI .for OR	
					Lower	Upper
Systolic blood pressure	0.033	0.014	0.020	1.033	1.005	1.062
Respiratory rate	-0.137	0.059	0.020	0.872	0.777	0.978
Glasgow coma scale	0.569	0.303	0.060	1.767	0.975	3.201
Renal dysfunction	2.122	0.749	0.005	8.345	1.923	36.213
Combined bioscore	2.367	0.810	0.003	10.661	2.179	52.165

DISCUSSION:

Sepsis is one of the principal causes of morbidity and mortality in critically ill patients. Fourteen day mortality rate observed among sepsis patients in our study was 41.9% (18/43).

Early diagnosis, risk stratification, predicting mortality of sepsis and appropriate antimicrobial therapy, remains the key to reduction in mortality and better outcome in such patients.

Several studies were conducted to assess the efficacy of individual biomarkers in diagnosis and predicting prognosis of sepsis with varying success.[4,5,6,9,11] Various authors had opined that combination of biomarkers would be more useful than a single one for risk stratification in sepsis.[5,12,13,14,15,16,17]

Hence we evaluated the efficacy of cheaper biomarkers in combination in predicting mortality in sepsis.. When we plotted and analysed our data under ROC curves, the area under curve (AUC) of the combined bioscore (by combining cheap individual biomarkers likeTLC, AEC, platelet count and CRP) was found to be significantly higher than that of individual biomarkers. This finding suggested that combined bioscore would be very useful in predicting 14 day mortality in sepsis patients.

On further analysis, combination of TLC, AEC and platelet count was noted to be the best in predicting mortality, with a sensitivity of 38.8 %, specificity of 96 %, positive predictive value (PPV) of 87.5 % and a negative predictive value (NPV) of 68.6 % , (p = 0.006).

Multivariate logistic regression analysis of factors predicting mortality also revealed combined bioscore as an independent predictor of 14 day mortality in patients with sepsis, with a very significant Odds Ratio of 10.661 (95 % CI, 2.179 – 52.165).

Combined biomarkers which we had analysed (TLC, AEC, platelet count and CRP) were very cheap, easy to assess and widely available. So they could be very useful in risk stratification and mortality prediction among sepsis patients in all health care levels, because of its availability and simplicity in assessment.

CONCLUSION

We observed that combined biomarkers (white cell count, absolute eosinophil count, platelet count and CRP) could serve as a valuable predictor of 14 day mortality in sepsis patients. Multivariate logistic regression analysis showed combined bioscore to be an independent predictor of mortality. Combined bioscore with the above mentioned cheap biomarkers would help to assess the severity of sepsis in all health care levels, that is from primary health care to tertiary care centre. Thus right antibiotic could be selected based on severity of sepsis. Hence development of antimicrobial resistance could be reduced and thus health care cost.

Limitations Of Our Study

1. Our sample size was small since the time frame of the study was limited to two months by Indian Council of Medical Research (ICMR).
2. We had done convenient sampling since to our knowledge there were no previous similar studies which had assessed the biomarkers which we had analysed.

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