ORIGINAL ARTICLE

Comparative Assessment of Cardiac Biomarkers and APACHE II Score for Prognostication in Septicemic Patients at a Tertiary Care Hospital

Shefali Meena[1], CL Nawal[2], Hazari L Saini[3], Radhey S Chejara[4*], Aradhana Singh[5]

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Abstract

Introduction: Cardiac dysfunction is one of the major causes of mortality in patients with sepsis. The acute physiology and chronic health evaluation II (APACHE II), quick sequential organ failure assessment (qSOFA), and other prognostic scores for sepsis have established data regarding their accuracy in predicting mortality. We have assessed the prognostic role of cardiac biomarkers [creatine phosphokinase-myocardial band (CPK-MB), troponin I (Trop I), and probrain natriuretic peptide (proBNP)] in patients with sepsis and compared it with the APACHE II score.

Materials and methods: A total of 126 patients (63 in each group) participated in this case–control study in a large tertiary care teaching hospital. Patients with sepsis who required hospitalization were enrolled in the case group and compared with another group of nonsepticemic patients. They were taken for detailed evaluation and investigation on day 1 and day 3. Our study included proBNP, CPK-MB, Trop I, and APACHE II score.

Results: Both the case and control groups comprised 63 patients each. It was observed that the cardiac biomarkers (proBNP, Trop I, CPK-MB) were markedly higher among cases than in controls. Similarly, these markers were also found markedly higher in fatal cases than survivors in the case group. Out of all three biomarkers, proBNP was correlated well with mortality as much as the APACHE II score. It was also observed that increasing trends in the levels of biomarkers depict prognosis more effectively than a single value.

Conclusion: We conclude that cardiac biomarkers can be routinely used as dynamic markers for the prediction of mortality and prognosis in patients with sepsis. ProBNP may be useful in predicting mortality in patients with sepsis.

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Introduction

Sepsis is an inflammatory reaction to infection that can result in organ failure and death.[1] Recent data showed that according to global estimates from 2017, sepsis affected approximately 48.9 million individuals and resulted in 11 million deaths, contributing to about 20% of total worldwide mortality.[2] This has led the World Health Organization (WHO) to acknowledge sepsis as a serious health concern and global health priority.

Circulatory impairment is a hallmark of severe sepsis and is exacerbated in septic shock. Complications of sepsis, such as cardiac dysfunction or septic organ dysfunction, most directly impacting the heart, can worsen the patient's health. Septic heart failure is widely acknowledged to increase the mortality risk in sepsis. What it looks like, how often it occurs, and what the long-term implications will be are all questions that remain unanswered.

Multiple pathways contribute to cardiac dysfunction in sepsis syndromes, including increased inflammation, energy loss, and reduced adrenergic signaling. Vascular permeability and endothelial dysfunction are both exacerbated by the activation of cytokines during the host immunological response to sepsis. These cytokines include interleukin-1 (IL-1), IL-8, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), IL-12, and IL-6.[3] The body's adrenergic response increases cardiac contractility and heart rate early in sepsis as a form of compensatory mechanism. In the long run, when oxidative stress levels rise, proapoptotic (β1 adrenergic receptors) and antiapoptotic (β2 adrenergic receptor) interactions become imbalanced, leading to overstimulation of β1 adrenergic receptors and subsequent myocardial damage and cell death.[4] The pathogenesis of sepsis-related cardiac dysfunction includes the energy imbalance of the organs brought on by sepsis. Because CD36, lipoprotein lipase, and lipoprotein remnant receptors are all downregulated, there is an increase in the quantity of lipoproteins in the blood that carry fatty acids and triglycerides.[5] Mitophagy also slows cardiac β-oxidation, leading to an accumulation of triglycerides intracellularly from unused fatty acids and ultimately a deficit in heart energetics.

Cardiac biomarkers in sepsis have been studied before, and many pathways leading to their appearance have been elucidated. Their association with mortality, cardiac dysfunction, and the progression of sepsis calls for additional studies, however. We compared the predictive ability of the acute physiology and chronic health evaluation II (APACHE II) score and three cardiac biomarkers in patients with septicemia: troponin I (Trop I), creatine phosphokinase-myocardial band (CPK-MB) isoform, and probrain natriuretic peptide (proBNP).

Materials and Methods

The present investigation was designed as a case–control study and was conducted in the Department of General Medicine at a tertiary care teaching hospital with a sample size of 126 patients (63 cases, 63 controls). Patients having sepsis who required hospitalization were enrolled in the cases group, while nonsepticemic patients were in the control group and evaluated accordingly. Participants were given a thorough explanation of the study's purpose, and after receiving their informed consent, the research was carried out.

Our study included CPK-MB, Trop I, proBNP, procalcitonin (PCT), and APACHE II scores. Other variables were hemoglobin, total leukocyte count (TLC), immature granulocytes (IG%), serum electrolytes, and serum creatinine. Patients were followed up for 28 days. Baseline cardiac biomarkers were done in cases and controls, and proBNP on day 3 was done in cases only.

For the statistical analysis, comparative analysis of quantitative data was performed

[1]Junior Resident; [2]Senior Professor; [3]Associate Professor; [4]Associate Professor; [5]Professor, Department of General Medicine, Sawai Man Singh Medical College, Jaipur, Rajasthan, India; *Corresponding Author

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using either the Mann–Whitney *U* test or the independent two-sample *t*-test, depending on data distribution. Categorical variables were evaluated using Fisher's exact test. All data were summarized as mean ± standard deviation (SD) or, when applicable, as percentages. Statistical significance was defined as a p-value < 0.05. The linear association between the APACHE II score and individual cardiac biomarkers was analyzed using the Pearson correlation coefficient.

Inclusion Criteria

Adults admitted to the hospital with sepsis.

Exclusion Criteria

Cardiothoracic events, long-term drug use, and pregnancy were all exclusion criteria. Patients with documented histories of chronic kidney disease, a systemic condition known to adversely affect heart performance, patients with fluid overload conditions such as severe anemia, or patients with central nervous system (CNS) disease who refused to participate in the study were excluded.

Observation and Results

Out of 63 cases, 35 (55.5%) were females and 28 (44.4%) were males, and out of 63 controls, 32 (50.7%) were males and 31 (49.2%) were females. Among 63 cases, the majority of individuals belonged to the 41–50-year age category, that is, 31 (49.21%). Among 63 controls, the majority of controls were in the age-group 41–50 years, that is, 27 (42.85%). There was a statistically significant difference in Trop I, CPK-MB, and proBNP levels on day 1 in cases and control groups (p-value 0.049, <0.0001, <0.0001, respectively) (Table 1).

Out of 63 patients in the cases group, 32 were nonsurvivors and 31 were survivors. The analysis demonstrated a statistically significant variation in the mean values of CPK-MB day 1 (p-value 0.0012), CPK-MB day 3 (<0.0001), proBNP day 1 (p-value 0.0350), and proBNP day 3 (p-value < 0.0001) in survivors and nonsurvivors among the cases group, while Trop I day 1 (p-value 0.2790) and day 3 (p-value 0.1065) were found nonsignificant (Table 2).

Pearson correlation analysis demonstrated significant positive associations between cardiac biomarkers and disease severity as measured by the APACHE II score. On day 1, Trop I (r = 0.234; p = 0.0649), CPK-MB (r = 0.507; p = 0.00002), and proBNP (r = 0.435; p = 0.0001) correlated with the APACHE II score. Similarly, on day 3, Trop I (r = 0.250; p = 0.0403), CPK-MB (r = 0.490; p = 0.00005), and proBNP (r = 0.727; p < 0.0001) maintained statistically significant correlations with the APACHE II score, with proBNP showing the strongest association.

A multivariate logistic regression model was applied to determine independent predictors of mortality among septicemic patients in the case group. The analysis revealed that elevated proBNP levels on day 1 (OR = 1.0001; p = 0.0511) and day 3 (OR = 1.0003; p = 0.0001), higher CPK-MB concentrations (OR = 1.0435; p = 0.0054), and increased APACHE II scores on day 1 (OR = 1.3413; p = 0.0001) and day 3 (OR = 1.3424; p = 0.0001) were significant predictors of mortality. These findings suggest that both biochemical markers and physiological scoring systems contribute meaningfully to mortality prediction in sepsis (Table 3).

With the exception of Trop I, all markers had area under the curves (AUCs) between 0.741 and 1 and were useful in identifying survivors from nonsurvivors on each day. The proBNP on day 3 was the best diagnostic measure for predicting nonsurvivors (AUC = 0.915) out of the five variables. The optimal cutoffs for proBNP day 1 were >2795, proBNP day 3 >3824, and CPK-MB >40.7. Correct prediction of nonsurvivors was achieved with a sensitivity of 84.4, 88.9, and

Table 1: Cardiac biomarkers among cases and controls

	Cases		*Controls*		*p-value*
	Mean	*SD*	*Mean*	*SD*	
Trop I	0.03	0.08	0.01	0.00	0.0494
CPK-MB	48.92	30.73	30.33	16.22	<0.0001
ProBNP (day 1)	7575.16	8445.52	255.73	140.82	<0.0001

Table 2: Cardiac biomarkers and APACHE II among survivors and nonsurvivors

	Nonsurvivors (N = 32)		*Survivors (N = 31)*		*p-value*
	Mean	*SD*	*Mean*	*SD*	
Trop I (day 1)	0.04	0.10	0.02	0.02	0.2790
Trop I (day 3)	0.04	0.10	0.01	0.02	0.1065
CPK-MB (day 1)	60.90	36.46	36.55	16.35	0.0012
CPK-MB (day 3)	57.62	22.6	34.66	15.23	<0.0001
ProBNP (day 1)	9770.44	9280.04	5309.06	6926.20	0.0350
ProBNP (day 3)	15456.67	10557.52	2389.65	3258.93	<0.0001
APACHE II (day 1)	33.44	5.29	27.00	3.92	<0.0001
APACHE II (day 3)	35.63	6.69	21.90	5.12	<0.0001

Table 3: Logistic regression analysis to predict predictors of mortality

Variable	*Coeff*	*Std err*	*p*	*OR*
ProBNP (day 1)	0.0001	0	0.0511	1.0001
ProBNP (day 3)	0.0003	0.0001	0.0001	1.0003
CPK-MB (day 1)	0.0425	0.0153	0.0054	1.0435
Trop I (day 1)	0.2658	12.0323	0.3936	2.29411
APACHE II score (day 1)	0.2936	0.0763	0.0001	1.3413
APACHE II score (day 3)	0.2945	0.0691	0.0001	1.3424

71.9% at these thresholds, while specificity ranged from 80.6 to 67.7% (Table 4).

The proBNP on day 3 was the best diagnostic measure for predicting nonsurvivors (AUC = 0.915) in cases out of the five variables (Fig.1).

Other significant variables included in our study are as follows—the mean arterial pressure (MAP) in cases is 70.29 and in controls 94.03. There was a highly significant difference in MAP between cases and controls ($p < 0.0001$), as well as between survivors and nonsurvivors ($p < 0.0001$). The mean APACHE II score demonstrated a reduction from 30.27 on day 1 to 27.39 on day 3, with a statistically significant difference between both groups ($p = 0.0289$). Moreover, within the case group, nonsurvivors had significantly higher mean APACHE II scores compared with survivors on both day 1 ($p < 0.0001$) and day 3 ($p < 0.0001$), indicating the strong prognostic value of this scoring system. In cases and controls, there is a statistically significant difference in mean TLC and IG% ($p < 0.0001$), while among survivors and nonsurvivors in the case group there is no statistically significant difference: TLC ($p = 0.4839$) and IG% ($p = 0.1249$).

A highly significant difference in serum PCT concentrations was observed between cases and controls ($p < 0.0001$), indicating its strong association with disease status, while among survivors and nonsurvivors there is no statistically significant difference.

Discussion

Sepsis still has a high fatality rate, comparable to that of myocardial infarction despite advances in treatment. Due to the elevated mortality observed in septic shock, cardiovascular dysfunction represents a characteristic and clinically significant manifestation among patients with severe sepsis. The cornerstone of sepsis care is, as always, early diagnosis and treatment.

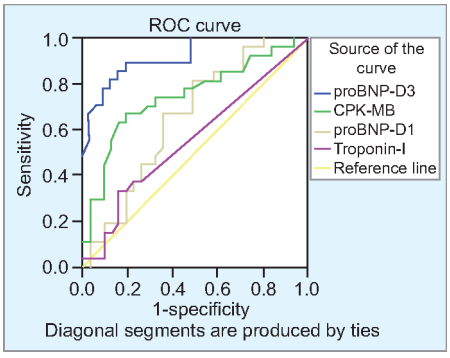

Fig. 1: ROC curve for APACHE II score and cardiac biomarkers

Raja et al.[6] conducted a study, "Cardiac biomarkers and myocardial dysfunction in septicemia." In the study, it was observed that troponin T (Trop T), CPK-MB, and NT proBNP were significantly elevated in patients with sepsis—mean values of 0.23 ± 0.8, 9.9 ± 13.4, and 5988.62 ± 13.7 pg/mL, respectively. In our study, similar results were seen; cardiac biomarkers were significantly elevated in cases as compared to controls—mean values of Trop I, CPK-MB, proBNP day 1, and proBNP day 3 are 0.03, 48.92, 7575.16, and 8472.57, respectively.

Papanikolaou et al.[7] conducted a study, "New insights into the mechanisms involved in BNP elevation and its role as an independent prognostic indicator in sepsis." The study demonstrated that the severity of sepsis was primarily associated with BNP elevation. A sustained elevation of BNP above 500 pg/mL provided a more reliable prediction of mortality than single-point BNP assessments. The inability to decrease BNP levels below 500 pg/mL was significantly associated with 28-day mortality, yielding an area under the receiver operating characteristic curve (AUROC) of 0.74 (95% CI: 0.55–0.93; $p = 0.03$), indicating moderate discriminatory accuracy. In our study, it was observed that out of three cardiac biomarkers, proBNP is the best diagnostic measure to predict nonsurvivors (AUC = 0.915, $p < 0.0001$, 95% CI: 0.84–0.98).

Yucel et al.,[8] in their study titled "The prognostic value of atrial and brain natriuretic peptides, Trop I and C-reactive protein in patients with sepsis," reported that BNP and APACHE II scores (AUC = 1.0) were the strongest diagnostic indicators for predicting nonsurvivors throughout the study period. On the 1st day, optimal cutoff values for BNP, cardiac troponin I (cTnI), and APACHE II were >32.1 pg/mL, >0.03 gm/L, and >23, respectively. On the 2nd day, the corresponding thresholds were >23.9 pg/mL, >0.03 gm/L, and >20, while on the final day, optimal cutoff values were >20.1 pg/mL, >0.03 gm/L, and >17, respectively. The diagnostic performance analysis demonstrated sensitivity rates of 100, 85, and 100% for accurate identification of nonsurvivors, accompanied by specificity rates of 100, 95, and 100% on respective study days. In our study, we observed the level of cardiac biomarkers and APACHE II scores on day 1 and day 3 of admission. With the exception of Trop I, all markers had AUCs between 0.741 and 1 and were useful in identifying survivors from nonsurvivors on each day. Among all observation days, the proBNP level measured on day 3 exhibited the greatest diagnostic efficacy for predicting mortality among septic patients out of the five variables (AUC = 0.915). The optimal cutoffs for proBNP day 1 were >2795, proBNP day 3 >3824, and CPK-MB >40.7. Correct prediction of nonsurvivors was achieved with a sensitivity of 84.4, 88.9, and 71.9% at these thresholds, while specificity ranged from 80.6 to 67.7%.

Witthaut et al.,[9] through their investigation "Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: impact of IL-6 and sepsis-associated left ventricular dysfunction," were the first to demonstrate a significant elevation in plasma BNP levels among patients with septic shock, suggesting a potential link between inflammatory mediators and cardiac dysfunction in sepsis. In our study, it was observed that high proBNP levels were associated with hospital stays of long duration and mortality.

Mehta et al.[10] conducted a study "Cardiac troponin-I predict myocardial dysfunction and adverse outcome in septic shock." The study included 37 consecutive patients who had septic shock. At study enrollment and 24 and 48 hours later, serum cTnI levels were assessed. Elevated serum cTnI was associated with a significantly higher dependence on inotropic and vasopressor agents, higher APACHE II score, regional wall motion abnormalities, lower ejection fraction, and higher mortality. Multivariate analysis revealed that serum cTnI, APACHE II score, anion gap, and serum lactate independently predicted both mortality and duration of intensive care unit (ICU) stay. Receiver operating characteristic curve analysis further confirmed the prognostic

Table 4: Calculated cutoff, sensitivity, specificity, and AUC values discharge/death

	AUC	*p-value*	*CI 95*	*Cutoff*	*Sensitivity*	*Specificity*
Trop I	0.597	0.185	0.456–0.738	0.025	38.4	83.9
CPK-MB	0.741	0.001	0.616–0.866	40.7	71.9	67.7
ProBNP (day 1)	0.701	0.006	0.572–0.830	2795	84.4	51.6
ProBNP (day 3)	0.915	<0.0001	0.844–0.986	3824	88.9	80.6

significance of serum cTnI as a reliable indicator of death in patients with septic shock. In our study, the receiver operating characteristics of Trop T were least significant with AUC (0.597); sensitivity and specificity of 38.4 and 83.9, respectively.

Berendes et al.,[11] in their work "Differential secretion of atrial and brain natriuretic peptide in critically ill patients," explored the secretion profiles of atrial and brain natriuretic peptides in individuals admitted to the ICU following major surgical interventions. Their findings indicated elevated plasma levels of these peptides among critically ill patients; however, no significant relationship was found between peptide concentrations and clinical outcomes. Conversely, Yin et al.,[12] in their retrospective study "Female-specific association of plasma N-terminal probrain natriuretic peptide (NT-proBNP) with organ dysfunction and prognosis in sepsis," demonstrated that elevated NT-proBNP levels were significantly associated with the occurrence of septic shock and increased 30-day mortality, particularly among female patients, suggesting a potential sex-specific prognostic value. In our study, it was observed that 28-day mortality was strongly associated with rising trends of proBNP rather than single-day value.

Perman et al.,[13] in their study "Relationship between B-type natriuretic peptide and adverse outcome in patients with clinical evidence of sepsis presenting to the emergency department," analyzed 825 patients and found that BNP had an AUC of 0.69 for predicting a triple composite outcome. The optimal predictive cutoff for BNP was identified as 49 pg/mL. Subjects with BNP concentrations above this threshold exhibited significantly higher rates of mortality, severe sepsis, and septic shock compared to those with lower levels. In our study, it was observed that except Trop I, proBNP and CPK-MB can be used as a diagnostic measure to predict nonsurvivors; AUC = 0.74 and 0.9, respectively. The sensitivity of CPK-MB was 71.9% (95% CI: 61–86%); specificity 67.7%. The sensitivity of proBNP on day 1 and day 3 was 84.4 and 88.9% (95% CI: 57–83 and 84–98%), respectively.

Chen and Li,[14] in their work "Prognostic significance of brain natriuretic peptide obtained in the emergency department in patients with systemic inflammatory response syndrome (SIRS) or sepsis," demonstrated that BNP positivity and 28-day mortality differed significantly between SIRS and non-SIRS groups. BNP levels correlated positively with APACHE II scores across all study groups. Furthermore, a BNP threshold >113 pg/mL emerged as an independent predictor of death among septic patients. In our study, it was observed that cardiac biomarkers were raised in cases as compared to controls, and there is a statistically significant Pearson correlation between Trop I ($r = 0.250$; p-value = 0.0403), CPK-MB ($r = 0.490$; p-value = 0.00005), and proBNP D1 ($r = 0.727$; p-value < 0.0001) and APACHE II score at day 3. Rising trends of BNP were more associated with an increased risk of mortality than any single value.

A study conducted by Amman et al.[15] entitled "Elevation of troponin I in sepsis and septic shock" measured cTnI levels in patients diagnosed with SIRS, sepsis, and septic shock. Elevated cTnI concentrations were found in 85% of the study cohort—comprising three patients with SIRS and nine with sepsis—while no elevation was detected among control participants (median 0.57 µg/L; range 0.17–15.4). In our study, cTnI levels were within the normal range in controls, while out of 63 cases, only 13 (5 survivors; 8 nonsurvivors) had raised cTnI levels.

Conclusion

In ICU settings, cardiac biomarkers (CPK-MB, proBNP, Trop I) show promise as a predictor of illness severity and mortality. ProBNP is the most reliable predictor of cardiac outcomes among the three biomarkers currently available. Time-series trends in proBNP are more informative than single readings, and it correlates as strongly with mortality as the APACHE II score does. It can be utilized as a dynamic marker of sepsis and is a cheap, quick test for diagnosis and prognosis in sepsis patients.

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