

RESEARCH ARTICLE

Do Cardiac Biomarkers Indicate Disease Severity and Predict Mortality in Septic Newborns?

Septik Yenidoğanlarda Kardiyak Biyobelirteçler Hastalığın Şiddetini Gösterir mi ve Mortaliteyi Öngörür mü?

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ABSTRACT

Objective: Sepsis is an important cause of morbidity and mortality in newborn infants. Cardiac involvement is also an important prognostic factor. Therefore, this study was aimed to investigate the relationship between the prognosis of neonatal sepsis and the levels of cardiac biomarkers such as cardiac troponin-I (cTnI) and creatine kinase-myocardial band (CK-MB).

Material and Method: Eighty-seven patients with culture-positive sepsis (Group I, n =26) or clinical sepsis (Group II, n =61) were enrolled the study. The control group (Group III) consisted of 42 non-septic healthy neonates. Demographic data and laboratory results of the cases were examined. Clinical outcomes (survival or death) were also recorded.

Results: No statistically significant difference was found between the groups in terms of gender, gestational age and birth weight. Six of eight septic patients (75%) with elevated cTnI died. Conversely, 13 of other septic patients (11%) with normal cTnI levels died. Hence, the mortality rate was statistically significantly higher in patients with elevated cTnI levels ($p < 0.001$). This study revealed that the cTnI cut-off value in neonates was 0.13 ng/ml (sensitivity 89.5%, specificity 90.9%). A 0.1-unit increase in cTnI level increased the risk of death by 1.4 times ($p = 0.012$). However, no statistically significant difference was observed between surviving and deceased patients in terms of CK-MB levels (15.8% and 11.8%, respectively) ($p > 0.05$).

Conclusion: There is a significant relationship between elevated cTnI levels and mortality in septic neonates. However, further multicenter studies with larger populations are needed to determine the relationship between cTnI levels and long-term prognosis in septic neonates.

Keywords: Heart Type Creatine Kinase Isoenzyme, Newborn, Prognosis, Sepsis, Troponin-I.

ÖZET

Amaç: Sepsis, yenidoğan bebeklerde önemli bir morbidite ve mortalite nedenidir. Kardiyak etkilenme önemli bir prognostik faktördür. Bu nedenle, kardiyak troponin-I (cTnI) ve kreatin kinaz-miyokardiyal bant (CK-MB) gibi kardiyak biyobelirteçlerin düzeyleri ile neonatal sepsis prognozu arasındaki ilişkinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Kültür pozitif sepsisli (Grup I, n =26) veya klinik sepsisli (Grup II, n =61) 87 hasta çalışmaya dahil edildi. Kontrol grubu (Grup III) septik olmayan 42 sağlıklı yenidoğan bebekten oluşuyordu. Olguların demografik verileri ve laboratuvar sonuçları incelendi. Klinik sonuçlar (sağkalım veya ölüm) da kaydedildi.

Bulgular: Gruplar arasında cinsiyet, gebelik yaşı ve doğum ağırlığı yönünden istatistiksel olarak anlamlı bir farklılık yoktu. Yüksek cTnI düzeylerine sahip sekiz septik hastanın altısı (%75) ölmüştü. Tersine, normal cTnI düzeylerine sahip diğer septik hastaların ise 13'ü (%11) ölmüştü. Buna göre, yüksek cTnI seviyelerine sahip hastalarda ölüm oranı istatistiksel olarak anlamlı derecede daha yüksekti ($p < 0.001$). Bu çalışmada yenidoğanlarda cTnI cut-off değerinin 0.13 ng/ml (duyarlılık %89.5, özgüllük %90.9) olduğu ortaya konulmuştur. Kardi-

yak TnI'da 0.1 ünitelik artış ölüm riskini 1.4 kat artırmaktaydı ($p = 0.012$). Buna karşın, hayatta kalan ve ölen hastalar arasında CK-MB düzeyleri yönünden istatistiksel olarak anlamlı bir farklılık saptanmadı (sırasıyla %15.8 ve %11.8) ($p > 0.05$).

Sonuç: Septik yenidoğanlarda cTnI yüksekliği ile mortalite arasında anlamlı bir ilişki vardır. Ancak, septik yenidoğanlarda cTnI düzeyleri ile uzun dönem prognoz arasındaki ilişkiyi belirlemek için daha fazla olgu sayısına sahip çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Kalp Tipi Kreatin Kinaz İzoenzimi, Yenidoğan, Prognoz, Sepsis, Troponin-I.

Neonatal sepsis refers to a systemic condition caused by bacterial, viral or fungal infections, characterized by hemodynamic changes and other clinical findings, leading to significant mortality and morbidity in newborn infants (1). Neonatal sepsis, which occurs in 1-8 per 1000 live births, can be classified into three groups according to the time of onset. Cases occurring within the first 72 hours of life are defined as early-onset neonatal sepsis (EOS), cases occurring after 72 hours of life are defined as late-onset neonatal sepsis (LOS), and cases occurring after a few weeks of life due to prolonged hospitalization of very low birth weight babies are defined as very late-onset neonatal sepsis (2). Microorganisms that play a role in the etiology of neonatal sepsis may differ among neonatal intensive care units (NICUs); different pathogens may be isolated at different times in the same unit and different antibiotic resistance may be observed (3). Definitive diagnosis is based on the isolation of the microbiological agent in body fluids such as blood and cerebrospinal fluid (CSF), which are normally sterile (1).

Multiple organ failure, an important finding in sepsis patients, is a clinical picture characterized by the deterioration of respiratory, liver, kidney, hematological and cardiac functions. Clinical and laboratory findings vary depending on the affected organ. Neonatal sepsis has high mortality rates and causes serious complications such as intraventricular hemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity, and neurodevelopmental disability (4). Hypotension and hypoperfusion due to cardiac dysfunction cause end-organ damage. Cardiac functions therefore affect all organ systems, and early detection of cardiac dysfunction and initiation of necessary treatments will contribute to prognosis (5).

In many studies, cardiac troponin I (cTnI) and creatine kinase-myocardial band (CK-MB) levels have been investigated as indicators of cardiac damage, especially in adults (5, 6). Some of these have shown that cTnI and CK-MB levels may be useful in demonstrating cardiac functions and predicting long-term prognosis (7, 8). Adult studies have found that cTnI levels are increased by 60% in septic patients with high mortality risks. Increased troponin levels have been associated with a 2- to 5-fold increased mortality risk even in septic patients without known cardiovascular disease (9). Cardiac TnI emerges in association with increased ventricular wall permeability and damage to cardiomyocytes

during sepsis-associated cardiac stress. It has been reported that cTnI and CK-MB biomarkers can be used to provide information about neonatal cardiac functions and can be helpful not only in the diagnosis stage but also in monitoring the response to treatment. Cardiac biomarker levels in neonates have been investigated in various diseases such as perinatal asphyxia, sepsis, congenital heart diseases and respiratory distress. Studies have shown that normal ranges of cTnI may vary depending on variables such as adaptation of cTnI to postnatal circulation, age, gender, measurement technique and kit used (10, 11). This situation limits the practical clinical use of cardiac biomarkers in newborn babies.

Therefore, this study aimed to investigate the relationship between cardiac biomarker (cTnI and CK-MB) levels and prognosis in septic neonates.

MATERIAL AND METHOD

The study was approved by our university's institutional clinical research ethics committee and the research was conducted in accordance with the principles of the Declaration of Helsinki (decision dated 08.12.2015 and numbered 21/04). This study was conducted in a Neonatal Intensive Care Unit (NICU) of Medical Faculty Hospital of Firat University. Our NICU has a total bed capacity of 45 beds, 15 of which are quaternary and 30 of which are tertiary, and the nurse-patient ratio is 1/3. The unit employs two neonatologists (professors of medicine), one neonatology subspecialty fellow, and two pediatric residents. The doctor/patient ratio 1/8.

Preterm (<37 gestational weeks) and term (>37 gestational weeks) newborns who underwent Töllner sepsis scoring due to suspicion of sepsis over a 46-month period between 2015 and 2018 and who met the inclusion criteria were prospectively enrolled in the study. Newborns with major congenital anomaly, inborn error of metabolism, congenital heart disease or cardiac dysrhythmia, asphyxia, those requiring short-term observation in the neonatal intensive care unit due to non-septic conditions (such as hypoglycemia, jaundice, transient tachypnea of the newborn, and other respiratory causes) were excluded from the study.

Patients with suspected sepsis were evaluated according to the "Töllner sepsis scoring" system (12). Accordingly, cases scoring <5 were evaluated as "not suspected sepsis", those scoring 5-10 as "sus-

pected sepsis”, and those scoring >10 as “probable sepsis”. Among the individuals in the probable sepsis group, those from whom bacteria were isolated in their blood cultures constituted the “proven sepsis” subgroup, and those from whom bacteria could not be isolated constituted the “clinical sepsis” subgroup. In addition, these patients were divided into groups I, II and III, respectively, as cases with bacterial isolation in blood culture or a Töllner sepsis score of >10 , cases with a Töllner sepsis score between 5 and 10, and non-septic healthy newborns with a Töllner sepsis score of <5 .

Neonatal sepsis was classified as EOS or LOS according to the time of onset. EOS describes neonatal sepsis that begins at ≤ 72 hours of life, while LOS describes neonatal sepsis that occurs at >72 hours of life (13). Infants born at <37 weeks of gestational age were considered preterm, and those born at ≥ 37 weeks were considered term neonates.

Demographic data (gestational age, postnatal age, gender, age at diagnosis), laboratory test results (complete blood count, C-reactive protein (CRP), cTnI, CK-MB, blood gas analysis and lactate) and culture-antibiogram results (blood, urine and CSF) were recorded in previously prepared study forms. The patient’s clinical outcomes (survival or death) and short- and long-term prognoses (epilepsy, neuromotor disability, vision-hearing problems, etc.) were also recorded.

Blood samples were taken and placed in 1 ml EDTA tubes and 1 ml dry tubes for sepsis evaluation. In addition to routine tests (for example, complete blood count, liver and kidney function tests and blood sugar, etc.), cTnI and CK-MB were investigated from blood samples placed in dry tubes. For micro CRP, 0.5 ml of blood was taken into a special pipette. About 0.5 ml blood was taken with a capillary blood gas pipette for blood gas analysis, and 2 ml blood sample was taken for blood culture. Micro CRP measurements were performed using a Quikread CRP device (Orion Diagnostica Oy, Espoo, Finland) installed in our unit. An ABL800 FLEX blood gas analysis device (Radiometer Medical ApS, Bronshøj, Denmark) was used for lactate and pH measurement. Complete blood count was performed with the ADVIA 2120i analyzer (Siemens AG, Erlangen, Germany). Creatine kinase-myocardial band and LDH were investigated with the ADVIA 2400 device (Siemens Healthcare GmbH, Nuremberg, Germany) and cTnI with the ADVIA Centaur XP device (Siemens Healthcare GmbH, Nuremberg, Germany). Creatine kinase-myocardial band values >40 U/L were considered positive and the reference range specified by our biochemistry laboratory was adopted. There is no limit that can be safely used in neonates. Studies to date for the cTnI reference range have yielded inconsistent results (10). Two studies with an upper

limit of 0.9 ng/ml for cTnI were accepted as reference for our study (9, 14, 15). BACTEC 9240 device (Becton Dickinson, New Jersey, USA) was used in the blood culture isolation procedures.

Statistical analysis

SPSS (Statistical Package for Social Sciences Windows version 22.0) software version was used for the statistical analysis. Descriptive statistics of continuous variables are presented as mean $\pm$ standard deviation. Normality controls for all variables were performed using the Shapiro-Wilk and Kolmogorov-Smirnov tests, and nonparametric methods were used in the analysis of variables that did not conform to normal distribution. The Mann-Whitney U test was used for two-group comparisons, the results being reported as Q1: first quartile, Q3: third quartile, and median values. Spearman’s correlation coefficient was used to determine linear relationships. The chi-square test was applied in the analysis of categorical variables. A 15-day trial version of MedClac software was used to determine cut-off values, while Statistica 11 software was used for all remaining analyses. Mann-Whitney U tests were used to compare median values and chi-square tests for percentages. One-Way Analysis of Variance (ANOVA) was applied to determined causes of differences in the comparison of non-parametric multiple variables. Statistical significance (p value) was determined as ≤ 0.05 for all analyses.

RESULTS

During the 46-month study period from February 2015 to December 2018, 986 patients were admitted to the NICU. Of these, 197 underwent Töllner sepsis scoring due to sepsis after hospitalization, and 129 patients who met the inclusion criteria were included in the study. Sixty-eight patients were excluded from study (26 due to neonatal jaundice, 16 due to transient tachypnea of the newborn/respiratory causes, 12 due to major congenital anomalies, 9 due to asphyxia, and 5 due to inborn error of metabolism).

The study included 87 septic patients (67.4%) (Group I + Group II) and 42 non-septic healthy neonates (32.6%) (Group III) admitted to the NICU of our hospital. Of the patients with clinical and laboratory findings suggestive of sepsis, 26 (29.9%) were in Group I (culture-proven sepsis) and 61 (70.1%) were in Group II (clinical sepsis). No statistically significant difference was observed between the groups in terms of gender, term-preterm ratio, gestational age and birth weight ($p > 0.05$) (Table 1).

Table 1. Comparison of patient groups according to their demographic characteristics.

	Group I (n: 26)	Group II (n: 61)	Group III (n: 42)
Female (n (%))	12 (46.2)	29 (47.5)	21 (50)
Male (n (%))	14 (53.8)	32 (52.5)	21 (50)
Term infants (n (%))	10 (38.5)	23 (37.7)	12 (28.6)
Preterm infants (n (%))	16 (61.5)	38 (62.3)	30 (71.4)
Gestational age (week) (Median (min-max))	36 (27-38)	35 (26-39)	34 (29-38)
Birth weight (g) (Median (min-max))	2080 (600-3330)	2160 (740-4000)	1750 (945-4000)

In terms of sepsis onset time, 13 (14.9%) patients were diagnosed with EOS and 74 (85.1%) patients were diagnosed with LOS. Blood culture was posi-

tive in 2 patients (15.3%) in the EOS group and in 24 patients (32.8%) in the LOS group. Accordingly, culture positivity in LOS cases was significantly higher than in EOS cases ($p < 0.001$). When all sepsis cases were evaluated together, regardless of the time of sepsis onset, the most frequently isolated microorganism from blood culture was coagulase-negative staphylococcus (*CoNS*). *Coagulase-negative staphylococcus* was isolated from one of the two patients in the EOS group, and *Klebsiella pneumoniae* was isolated from the other. In terms of laboratory parameters, no significant difference was observed between the groups in terms of white blood cell (WBC) count and CK-MB levels, while significant differences were found between platelet count, CRP, lactate, and cTnI levels and pH value (Table 2).

Table 2. Comparison of laboratory results between patient groups.

Variables	Group I Median (Min-Max)	Group II Median (Min-Max)	Group III Median (Min-Max)	P ^Σ
[‡] WBC ($\times 10^3/\text{mm}^3$)	13.3 (4.1-24.9)	12.3 (6.9-35.8)	11.0 (3.5-29.4)	=0.400
Platelet ($\times 10^3/\text{mm}^3$)	81 (14-382)	221 (7-809)	237 (113-342)	<0.001*
#CRP (mg/L)	149 (25-238)	62 (3-192)	3 (3-18)	<0.001*
Lactate (mmol/L)	2.4 (1.6-9)	2 (0.8-7)	0.8 (0.4-3.5)	<0.001*
pH	7.28 (7.17-7.36)	7.32 (7.18-7.42)	7.34 (7.28-7.42)	<0.001*
[‡] CK-MB (IU/L)	69 (19-507)	57 (19-688)	54 (15-575)	=0.598
Troponin-I (ng/mL)	0.085 (0.01-5.23)	0.05 (0.01-1.27)	0.02 (0.01-0.27)	<0.001*

[‡]WBC, White blood cell; #CRP, C-reactive protein; [‡]CK-MB, Heart type creatine kinase isoenzyme, ^ΣKruskal-Wallis test; *Statistically significant ($p < 0.05$).

Mortality rates in cases with high and normal CK-MB levels were 15.8% and 11.8%, respectively. Hence, no significant correlation was found between CK-MB levels and mortality rate ($p > 0.05$). Median cTnI levels were 0.03 ng/mL (range, 0.01-

1.27) in surviving patients and 0.267 ng/mL (range, 0.030-5.230) in deceased patients. In fact, cardiac TnI levels were significantly higher in deceased patients ($p < 0.001$) (Table 3).

Table 3. “Cut off” values to predict the effects of laboratory parameters on mortality.

Variables	Cut-off value	Sensitivity	Specificity	Negative Predictive value	Positive Predictive value	AUC
Troponin (ng/mL)	0.13	89.47	90.91	98.04	62.91	0.916*
#CK-MB (IU/L)	74	87.89	69.09	89.22	19.99	0.591
Lactate (mmol/L)	1.6	21.05	100.00	88.02	100.00	0.820*
Platelet ($\times 10^3/\text{mm}^3$)	147000	73.68	74.55	94.26	33.28	0.737*
[‡] WBC ($\times 10^3/\text{mm}^3$)	8640	47.37	76.36	89.38	25.66	0.582

#CK-MB, Heart type creatine kinase isoenzyme, [‡]WBC, White blood cell, *AUC, Area under the ROC curve.

A significant effect of troponin value on mortality was found ($p = 0.012$). It was found that a 0.1-unit increase in cTnI level increased the risk of death by 1.4 times (95% confidence interval 0.48-4.18). The specificity and sensitivity of cTnI and CK-MB in determining sepsis severity are shown in Figure 1 and Figure 2.

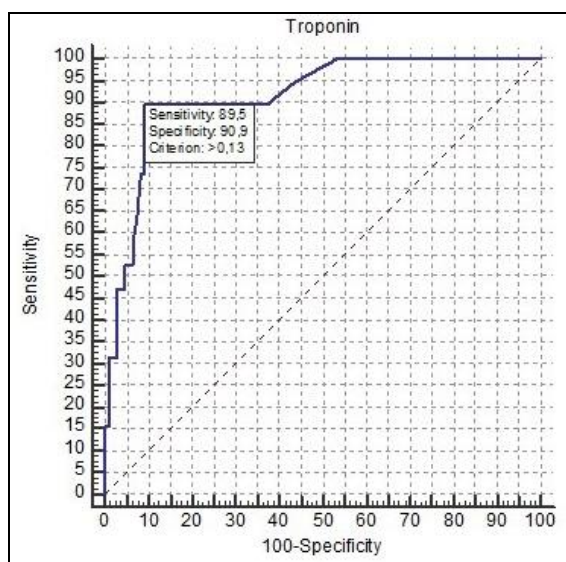


Figure 1. Specificity and sensitivity of cTnI in predicting the severity of neonatal sepsis.

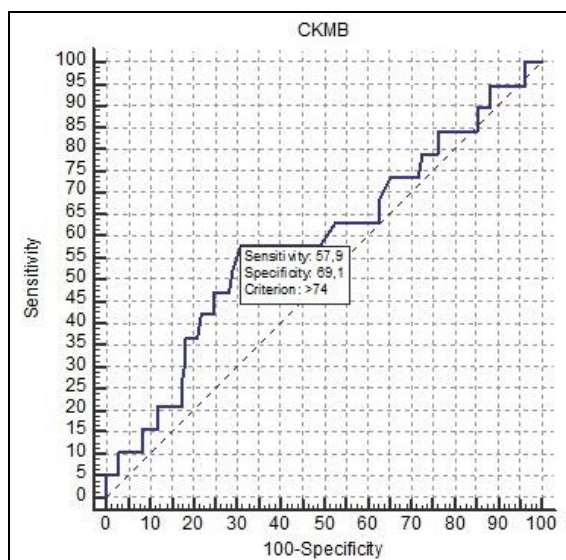


Figure 2. Specificity and sensitivity of CK-MB in predicting the severity of neonatal sepsis.

Similarly, lactate level was also found to have a significant effect on mortality risk ($p=0.025$). Additionally, a significant difference was observed between surviving and deceased patients in terms of CRP level ($p<0.001$), platelet count ($p=0.001$) and pH value ($p<0.001$). Table 4 shows the effects of laboratory parameters on mortality.

Table 4. Effects of laboratory parameters on mortality.

Variables	Odds Ratio (%95 CI)	P value
Troponin I (ng/mL)	1412.658 (4.774 - 418042.543)	0.012*
#CK-MB (IU/L)	1.006 (0.994 - 1.017)	0.346
‡CRP (mg/L)	1.003 (0.985 - 1.021)	0.762
Lactate (mmol/L)	2.612 (1.127 - 6.052)	0.025*
&WBC ($\times 10^3/\text{mm}^3$)	1.000 (1.000 - 1.000)	0.873
Platelet ($\times 10^3/\text{mm}^3$)	1.000 (1.000 - 1.000)	0.136

#CK-MB, Heart type creatine kinase isoenzyme; ‡CRP, C-reactive protein; ‡LDH, Lactate dehydrogenase, &WBC, White blood cell, *Statistically significant ($p<0.05$).

DISCUSSION

Thanks to developing technology and antimicrobial treatments, the probability of survival of premature and low birth weight babies has increased. However, supportive approaches (total parenteral nutrition, etc.), interventional procedures (intubation, central catheter insertion, etc.) and developing complications (ventilator associated pneumonia, etc.) increase the risk of neonatal sepsis, which is a significant cause of mortality and morbidity. Many cytokines have been shown to play a role in the pathogenesis of sepsis, which may help predict prognosis. The role and prognostic value of tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), interleukin-10 (IL-10) and procalcitonin in sepsis pathophysiology have been investigated in numerous studies (14-16). However, there is no test yet that can accurately predict the severity and prognosis of the disease in septic neonates. Therefore, this study aimed to investigate whether cardiac biomarkers cTn-I and CK-MB are determinants of prognosis in septic newborn cases.

Although the areas of use and reference ranges of cardiac biomarkers are well defined in adults, they are not yet clear in neonates. Biomarkers of myocardial damage can be detected from blood tests and these markers may develop not only in the disease state but also due to prenatal and postnatal causes such as exposure to acute or prolonged tocolytic therapy and physiological circulatory changes after birth. Studies have shown that cardiac troponin limits in healthy newborns are higher than in adults due to the factors mentioned above (17, 18). Creatine kinase-myocardial band, which is mostly of muscular origin and reflects perinatal stress or tissue damage, does not provide clear results about the stage of myocardial damage in the neonates, especially in the first days of life. However, increases in cardiac troponin above a certain physiological level may indicate myocardial involvement. Intracellular protein leakage and damage to the myocardial cell membrane are thought to be an important mechanism for blood cTnI levels (19). Cardiac biomarkers

have been studied in many diseases such as perinatal asphyxia, patent ductus arteriosus, persistent pulmonary hypertension, sepsis and bronchopulmonary dysplasia to determine the severity of the disease and to predict the prognosis (20).

Myocardial dysfunction caused by sepsis is a result of hemodynamic, molecular, metabolic and structural changes and is closely related to sepsis-related mortality and morbidity (21, 22). Increased cTnI levels are a common finding in patients with sepsis. In these cases, coronary angiography and autopsy results have shown that high cTnI may occur without significant findings in favor of coronary artery disease (23). Peek et al. (24) examined the levels of cTnI, cardiac troponin T (cTnT), creatinine kinase (CK) and CK-MB in newborn calves with experimentally induced sepsis with *E. coli* endotoxin. These researchers found a significant difference in cTnI and CK levels measured after endotoxemia compared to control and baseline levels. Oliveira et al. (25) examined the effect of cTnI levels on survival in pediatric patients diagnosed with sepsis and septic shock and identified serum cTnI levels as the only variable associated with the severity of septic disease and mortality. In that study, CK-MB levels did not appear to have any effect on survival.

Abdel-Hady et al. (6) demonstrated the diagnostic and prognostic use of cTnT and “total ejection isovolumic index (Tei)” in patients with sepsis. A positive correlation was observed between left and right ventricular Tei index and cTnT levels in patients with neonatal sepsis. Cardiac TnT concentrations and left ventricular Tei index were significantly higher in septic neonates who died than in survivors. Frencken et al. (26) evaluated the relationship between cTnI levels and sepsis-related mortality and long-term (one-year) outcomes in septic patients. These researchers reported that increases in cTnI levels were associated with increased mortality rates in the first 14 days after sepsis, but not in subsequent days. An association between increased cTnI levels during sepsis and long-term cardiovascular disease in patients who survived a septic episode has been reported, and this association may predict cardiovascular morbidity after discharge.

Cardiac TnI levels, a sensitive marker of cardiac damage, were found to be significantly higher in the sepsis group in this study, and the mortality rate was correspondingly higher in patients with elevated cTnI levels. Previous studies have shown that cTnI levels can provide useful information about long-

term prognosis. For example, Zheng et al. (27) reported that elevated troponin levels in sepsis patients are a potential predictor of prognosis, including hospital and long-term mortality. Moreover, the researchers recommended that clinicians treating septic patients with elevated troponin levels should be more careful to avoid extra death. However, conflicting results have been reported regarding whether CK-MB levels can predict prognosis in neonatal diseases. Beydilli and Gökçe (28) demonstrated that increases in serum cardiac biomarkers such as CK-MB, cTnI and NT-proBNP in newborn calves were indicative of sepsis-induced cardiac damage and dysfunction. In contrast, Kırbas et al. (29) reported that CK-MB had low diagnostic performance than cTnI in detecting myocardial injury in newborn calves with sepsis. In our study, no significant difference was found between the sepsis group and the control group in terms of CK-MB levels. Similarly, no significant difference was found in mortality rates in patients with high CK-MB levels. In this study, the cTnI cut-off value was found to be 0.13, and a 0.1-unit increase in cTnI level increases the risk of mortality by 1.4 times.

The limitations of this study include the use of micro CRP in our unit and the fact that cytokines or biomarkers such as procalcitonin and IL-6 are not routinely studied in our hospital and therefore they were not included in our study. In addition, echocardiographic examination was not performed simultaneously with cTnI levels in all patients. Another limitation is that the relationship between cTnI levels and short-term complications and long-term sequelae could not be evaluated. Additionally, stronger results could have been obtained by including a larger number of patients in the study. A final limitation is that the results reflect those of only one center.

Conclusion

Neonatal sepsis is an important health problem in neonates with high mortality rates. Cardiac TnI is a marker that can give an idea about the risk of death in patients with neonatal sepsis. However, the importance of CK-MB in predicting mortality in neonatal sepsis is controversial. Multicenter studies with larger populations are needed on the importance of cardiac biomarkers in predicting long-term prognosis in septic neonates.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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