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# Troponin-T value as a prognostic marker in neonates diagnosed with neonatal encephalopathy and receiving hypothermia treatment

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**Abstract. – OBJECTIVE:** The aim of this study was to investigate the effect of Troponin-T levels on the prognosis of neonatal encephalopathy (NE).

**PATIENTS AND METHODS:** The study included one hundred and eleven newborns diagnosed with NE and receiving hypothermia treatment. The cases were separated into 2 groups according to the SARNAT classification as Stage 2 or Stage 3. The groups were compared in respect of anthropometric characteristics, APGAR scores, and biochemical parameters. The cases were also separated into 3 groups according to the Troponin-T levels and were compared with respect to the clinical course.

**RESULTS:** The serum Troponin-T ( $p=0.012$ ), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ( $p<0.0001$ ), and lactate levels ( $p=0.04$ ) in the Sarnat Stage 3 group were statistically significantly higher than in the Sarnat stage 2 group. A significant positive correlation was determined between the Troponin-T level and the total duration of respiratory support ( $r=0.20$ ,  $p=0.03$ ). A significant positive correlation was determined between the ALT/AST ratio and the length of stay in hospital ( $r=0.29$ ,  $p=0.001$ ), duration of intubation ( $r=0.32$ ,  $p=0.01$ ), and total duration of respiratory support ( $r=0.36$ ,  $p<0.001$ ). A statistically significant difference was determined in mortality rates between the 3 subgroups of Troponin-T levels; Group 1: 2.8%, Group 2: 5.4%, and Group 3: 15.8%. ( $p=0.04$ ,  $\chi^2=4.74$ ). A cut-off value of 164 ng/L for Troponin-T was determined to predict mortality with 77% sensitivity and 67% specificity (AUC=0.73,  $p=0.023$ ). When the groups were compared according to Troponin-T level, a statistically significant difference was determined in respect of length of stay in hospital ( $p=0.03$ ,  $\chi^2=6.95$ ) and total duration of oxygen support ( $p=0.01$ ,  $\chi^2=9.12$ ).

**CONCLUSIONS:** The serum Troponin-T level can be evaluated as a prognostic marker in cases followed up with a diagnosis of NE and receiving hypothermia treatment. There is a need for further prospective studies with larger samples on this subject.

*Key Words:*

Newborn, Neonatal Encephalopathy, Asphyxia, Hypothermia, Troponin-T.

## Introduction

Neonatal encephalopathy (NE) is a multisystemic complex condition that manifests neurological impairment in infants due to many etiologies such as infections, hypoxia, ischemia, genetic factors, and metabolic abnormalities<sup>1</sup>. Despite improvements in maternal and neonatal care, perinatal asphyxia-related NE remains a significant cause of morbidity and mortality. The frequency is approximately 1-6 per 1,000 live births<sup>2,3</sup>. The mortality rate has been reported to vary between 8.7% and 33.3%<sup>4</sup>. However, studies<sup>5</sup> have shown that starting hypothermia treatment (33-34°C) within the first 6 hours has reduced morbidity and mortality rates.

Myocardial dysfunction associated with hypoxia and decreased myocardial perfusion is often seen in cases with perinatal asphyxia. In addition to disrupted myocardial perfusion, accompanying sepsis, persistent pulmonary hypertension, and acute kidney failure are also known to cause myocardial dysfunction<sup>6</sup>. This effect has been reported to vary between 24% and 78% in cases with asphyxia<sup>7-10</sup>. Cardiac

Troponin-T is a component of the tropomyosin complex, which regulates cardiac muscle contractility. Compared to creatine kinase MB (CK-MB), Troponin-T increases earlier in myocardial damage and remains high for longer in the blood<sup>11</sup>. On the other hand, it is known to be more specific to the heart muscle than CK-MB<sup>12</sup>.

There is a limited number of studies in the literature investigating the association between Troponin-T level and cardiac morbidity and mortality in newborns with asphyxia<sup>6,13-20</sup>. However, with the exception of one study that focussed on the relationship between the Troponin-T level and acute renal damage, no studies in the literature have investigated the effect of the Troponin-T level on non-cardiac prognosis<sup>21</sup>.

The primary aim of this study was to investigate the relationship between the Troponin-T level and mortality, length of stay in hospital, respiratory support requirement characteristics, the time to start feeding, and laboratory parameters in newborn infants diagnosed with perinatal asphyxia and receiving hypothermia treatment.

## Patients And Methods

The study included one hundred and eleven newborn infants with NE who were followed up in the neonatal intensive care unit (NICU) and underwent hypothermia treatment between February 1, 2019, and August 1, 2022. The indications for hypothermia treatment because of hypoxic-ischaemic encephalopathy were<sup>2,22</sup>:

- Gestational age of  $\geq 36$  weeks.
- In the first 6 hours of life.
- Cord blood gas pH  $\leq 7.00$  or base deficit (BD)  $\leq -16$  mmol/L.
- 10-min APGAR score  $< 5$  or a continuing need for resuscitation.

Infants with a major congenital anomaly, a metabolic disease, or birthweight  $< 2,000$  gr were excluded from the study.

From the electronic files of the patients included in the study, gender, maternal age, gestational week, birthweight, length, head circumference, mode of delivery, and APGAR scores were recorded. During the first three days of hospitalization, the following parameters were evaluated every 12 hours; hemogram (CBC), blood gas, alanine aminotransferase (ALT) aspartate aminotransferase (AST), creatine kinase (CK), CK-MB, and Troponin-T. The highest levels were recorded for the statistical evaluations.

The cases were separated into 2 groups according to the Sarnat classification as Stage 2 or Stage 3. The patients were also separated into 3 groups according to the Troponin-T level percentiles, Group 1 ( $\leq 99.17$  mg/dl), Group 2 ( $99.17$  mg/dl  $<$  Troponin-T  $< 180.60$  mg/dl), and Group 3 ( $\geq 180.60$  mg/dl).

The ALT and AST values were examined using a hemogram XN-9000 device (Sysco Co., Kobe, Japan), the CK parameters with a Cobas 8000 device (Roche Diagnostics, Mannheim, Germany), the CK-MB and Troponin-T parameters with a Roche Cobas e411 device, and blood gas with an ABL-90 FLEX analyzer (Radiometer Medical Aps, Denmark).

## Statistical Analysis

With the inclusion of 111 patients,  $\alpha=0.05$ ,  $\beta=0.10$ , and  $1-\beta=0.10$ , the test power was found to be 0.90005. The data obtained in the study were analyzed statistically using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). The conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. In comparing measurements obtained from two or three independent groups, the Mann-Whitney U-test or Kruskal-Wallis tests were applied, and the Chi-square test was used for categorical data. Relationships between variables were determined with correlation analysis, and ROC curve was formed to determine the optimal cut-off value of Troponin-T in showing prognosis. Data were stated as the median and interquartile range (IQR) values or number (n) and percentage (%). A value of  $p < 0.05$  was accepted as statistically significant.

## Results

A total of 111 neonates were evaluated, with 93 (84%) at Sarnat Stage 2 and 18 (16%) at Sarnat Stage 3. No significant difference was determined between the Sarnat stage groups with respect to the gestational age, gender, maternal age, birthweight, length and head circumference, C/S rates, and rates of resuscitation ( $p > 0.05$ ). The rate of surfactant administration (38.9% vs. 4.3%) and the mortality rate (38.9% vs. 2.2%) were determined to be significantly higher in the Sarnat Stage 3 group than in the Stage 2 group ( $p < 0.001$  for both). The 1-minute APGAR score [4 (3) vs. 2.5 (4)] and 5-min APGAR score [7 (3) vs. 5 (2)] were determined to be significantly lower in the Sarnat Stage 3 group ( $p=0.004$ ,  $p=0.002$ , respectively). The sociodemographic data of the Sarnat Stage 2 and Stage 3 patients are shown in Table I.

## Troponin-T values in neonatal encephalopathy

**Table I.** Baseline characteristics of Sarnat Stage 2 and Stage 3 in newborns with hypoxic-ischemic encephalopathy\*.

	Stage 2 (n=93)	Stage 3 (n=18)	Total (n=111)	p
Gestational age (week)	39 (2)	39 (2.7)	39 (2)	0.19
Gender (%Female)	39 (41.9)	7 (38.9)	46 (41.4)	0.51
Maternal age (year)	27 (7)	30.5 (12.5)	27 (8)	0.12
Birth weight (gram)	3,200 (650)	3,275 (869)	3,200 (695.0)	0.68
Birth size (cm)	49 (3.5)	49.5 (5.25)	49 (4)	0.85
Head circumference (cm)	35 (2)	34.5 (4)	35 (2)	0.37
% C/S	27 (29)	9 (50)	36 (32.4)	0.08
AGA	81 (87.1)	13 (72.2)	94 (84.7)	
SGA	6 (6.5)	2 (11.1)	8 (7.2)	0.24
LGA	6 (6.5)	3 (16.7)	9 (8.1)	
Neonatal Resuscitation	77 (82.8)	17 (94.4)	94 (84.7)	0.29
Surfactant Administration	4 (4.3)	7 (38.9)	11 (9.9)	<0.0001
Death	2 (2.2)	7 (38.9)	9 (8.1)	<0.0001
APGAR scores 1. Minute	4 (3)	2.5 (4)	4 (3)	0.004
APGAR scores 5. Minute	7 (3)	5 (2)	6 (3)	0.002

\*Data were given as median (IQR) or n(%). C/S: Cesarean section AGA: Appropriate for gestational age, SGA: Small for gestational age, LGA: Large for gestational age.

The serum Troponin-T ( $p=0.012$ ), ALT and AST ( $p<0.0001$ ), and lactate levels ( $p=0.04$ ) in the Sarnat Stage 3 group were statistically significantly higher than in the Sarnat Stage 2 group. The thrombocyte count was seen to be lower in the Stage 3 cases ( $p=0.002$ ). The laboratory findings of the Stage 2 and Stage 3 cases are shown in Table II.

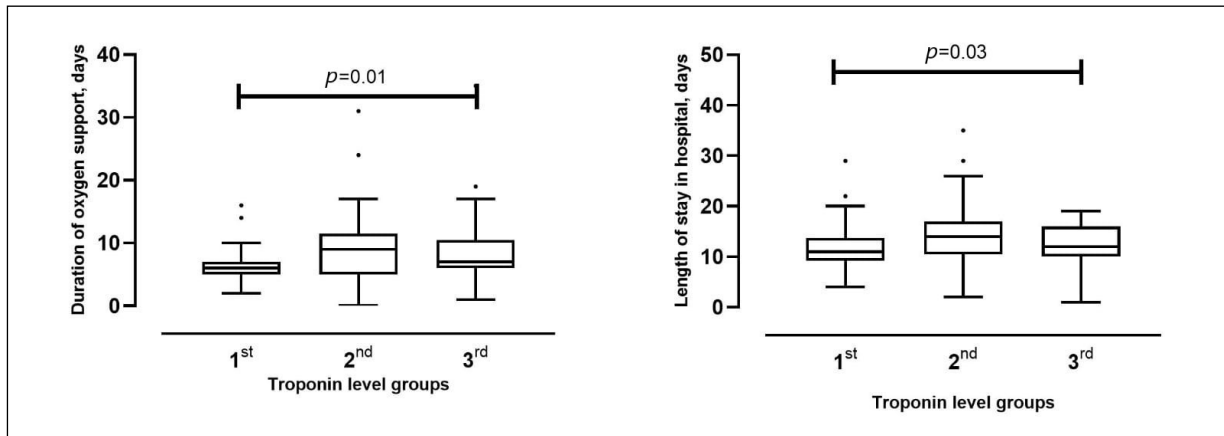
Troponin-T levels were positively correlated with the total duration of respiratory support ( $r=0.20$ ,  $p=0.03$ ). The ALT/AST ratio also had also correlated with the length of hospital stay ( $r=0.29$ ,  $p=0.001$ ), duration of intubation ( $r=0.32$ ,  $p=0.01$ ), and overall duration of respiratory support ( $r=0.36$ ,  $p=0.001$ ). At the same time, there was a negative correlation between thrombocyte count and intubation length ( $r=-0.20$ ,  $p=0.027$ ).

When the Troponin-T level groups were compared, a statistically significant difference was determined in respect of the length of stay in hospital ( $p=0.03$ ,  $\chi^2=6.95$ ) and total duration of oxygen support ( $p=0.01$ ,  $\chi^2=9.12$ ). The length of stay in the hospital and duration of oxygen support were determined to be longer in Group 2 and Group 3. In the post-hoc tests (Tamhane), the difference originated from Group 1 (Figure 1). On the other hand, a statistically significant difference was determined in mortality rates between the 3 subgroups of Troponin-T levels; Group 1: 2.8%, Group 2:5.4%, and Group 3: 15.8%. ( $p=0.04$ ,  $\chi^2=4.74$ ). A cut-off value of 164 ng/L for Troponin-T was determined to predict mortality with 77% sensitivity and 67% specificity (AUC =0.73,  $p=0.023$ ) (Figure 2). However, the time to

**Table II.** Laboratory parameters of Sarnat Stage 2 and Stage 3 in newborns with hypoxic-ischemic encephalopathy\*.

	Stage 2 (n=93)	Stage 3 (n=18)	p
Troponin-T (ng/L)	124.6 (122.61)	250.6 (768.47)	0.012
CK (U/L)	2,455 (2,531.75)	3,379 (4,160)	0.43
CK-MB (ug/L)	76.6 (79.98)	111.7 (153.68)	0.18
ALT (U/L)	27 (19.25)	64 (88.5)	0.0001
AST(U/L)	91 (50.25)	170 (215)	0.0001
ALT/AST	0.28 (0.17)	0.43 (0.40)	0.05
pH	6.98 (0.12)	6.95 (0.20)	0.28
Lactate (mmol/L)	10 (4.78)	11.5 (4)	0.04
HCO <sub>3</sub> (mmol/L)	15 (4.82)	13 (9.45)	0.11
BE (mmol/L)	-16 (5.25)	-17.4 (11.7)	0.16
WBC (10 <sup>9</sup> /L)	20,885 (7,225)	21,900 (14,330)	0.38
Thrombocyte (10 <sup>9</sup> /L)	165,500 (68,750)	107,000 (90,000)	0.002
Hemoglobin (g/dL)	17.25 (2.83)	17.6 (2.95)	0.35

\*Data were given as median (IQR). HCO<sub>3</sub>: Bicarbonate, BE: Base excess, WBC: White Blood Cell.



**Figure 1.** Length of stay in hospital and total duration of oxygen support according to Troponin-T level groups.

oral feeding, total duration of respiratory support, duration of intubation, and duration of non-invasive ventilation were similar ( $p=0.05$ ) according to Troponin-T level groups (Table III).

### Discussion

The main findings of this investigation were that the mortality rate was greater in the group with a high Troponin-T level. Additionally, the Troponin-T level was seen to statistically significantly affect the length of stay in hospital, and the duration of oxygen support. Finally, as expected, Troponin-T, ALT, AST, and lactate levels were higher, and platelet counts were lower in the Sarnat Stage 3 group.

In addition to the brain, the heart, kidneys, liver, and several other organs are affected by perinatal hypoxia<sup>23</sup>. The mortality rate in patients with perinatal asphyxia has been reported at rates varying from 14% to 74% in different studies<sup>4,13,17-18</sup>. The variations in mortality data could be the result of changes in case management and treatment over time, or they could be the result of variations in the study centers. In accordance with the literature, the mortality rate in the current

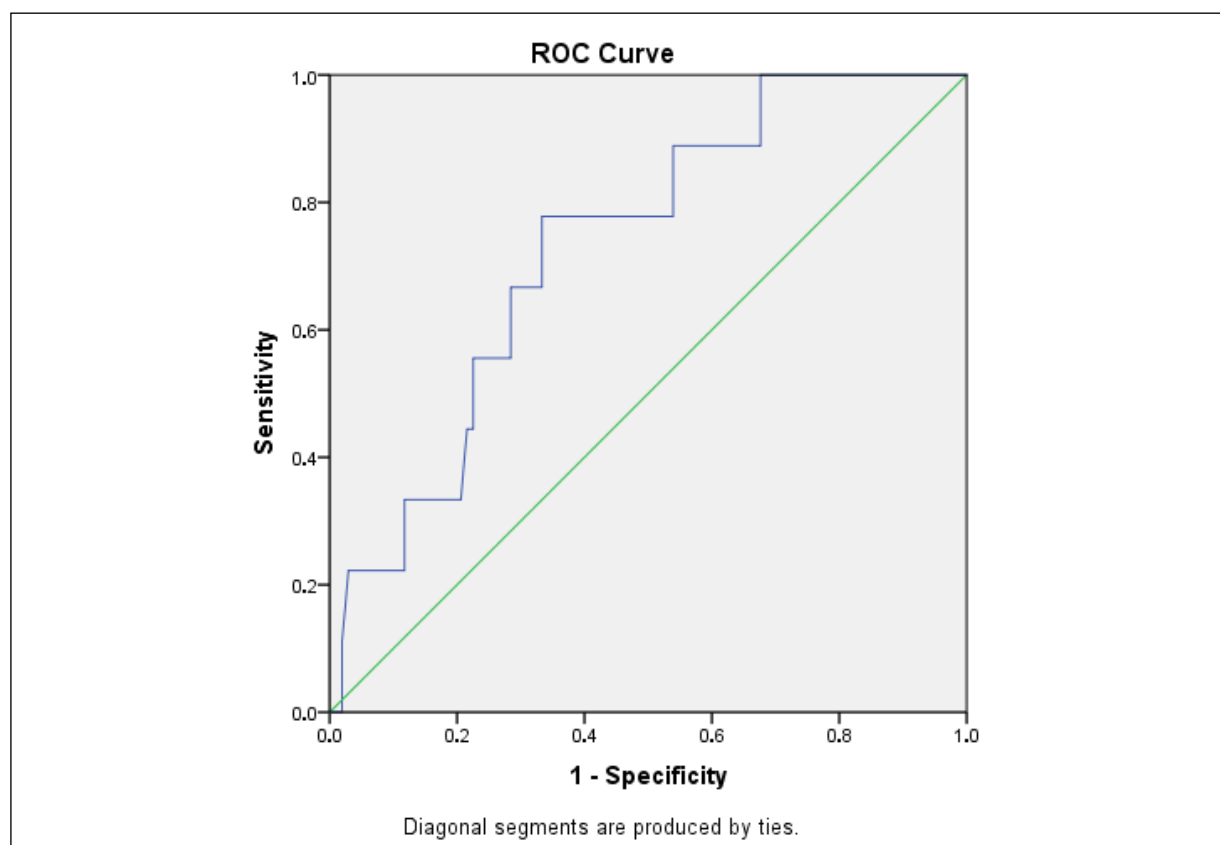
study was found to be 38.9% in the Stage 3 group, 2.2% in the Stage 2 group, and 8.1% overall.

Evaluation of the severity of neonatal encephalopathy and the early determination of the damage in each system is crucial for the management of NE and will reduce morbidity and mortality rates<sup>13</sup>. Various biomarkers have been studied to detect organ damage in patients receiving therapeutic hypothermia treatment with a diagnosis of NE<sup>24,25</sup>. Cardiac damage has been reported to be a major cause of mortality in these patients<sup>26</sup>. Therefore, studies have been conducted on the early detection and treatment of cardiac damage. Troponin-T is one of the most investigated cardiac-specific isoenzymes in cases with perinatal asphyxia<sup>27</sup>. The American Cardiology Academy and European Cardiology Association have reported that Troponin-T is the best marker of myocardial damage<sup>28</sup>. Studies of the pediatric age group have also determined that the Troponin-T value is more sensitive and specific than the CK-MB value in the determination of cardiac damage<sup>29</sup>. In the majority of studies<sup>7-10,17,20,30,31</sup> of neonates with asphyxia, cardiac dysfunction has been determined at the rate of 24-78%. Michniewicz et al<sup>13</sup> determined that the Troponin-T value was

**Table III.** Comparison of clinical findings according to troponin levels in newborns with hypoxic-ischemic encephalopathy\*.

	Group 1 (n=36)	Group 2 (n=37)	Group 3 (n=38)	p	χ <sup>2</sup>
Length of stay in hospital	11 (4)	14 (6)	12 (6)	0.03	6.95
Total duration of oxygen support	6 (2)	9 (6)	7 (4)	0.01	9.12
The time to full oral feeding	9 (2)	9 (2)	9 (3)	0.32	2.26
Total duration of respiratory support	4 (3)	4 (6)	5 (5)	0.11	4.38
Duration of intubation	1 (3)	1 (4)	2 (3)	0.14	3.92
Duration of non-invasive ventilation	2 (3)	3 (3)	2 (3)	0.73	0.62

\*Data were given as median (IQR)



**Figure 2.** ROC curve for the optimal cut-off value of Troponin-T on mortality.

4-fold higher in cases with severe asphyxia compared to those with asphyxia at a moderate level. Joseph et al<sup>18</sup> showed that the Troponin-T level was correlated with the severity of asphyxia and mortality, and could therefore be an early biomarker for mortality. In a study of patients followed up for perinatal asphyxia and treated with hypothermia, Liu et al<sup>32</sup> found that Troponin-T levels decreased with treatment and that those with low Troponin-T levels had better outcomes. Another study by Yellanthoor and Rajamanickam<sup>16</sup> found that Troponin-T levels correlated with ECHO findings, need for inotrope support, severity of asphyxia and mortality. Similarly, Bhasin and Kohli<sup>17</sup> found a correlation between Troponin-T levels and the severity of asphyxia and cardiac effects. Yang et al<sup>20</sup> showed that umbilical cord blood Troponin-T was significantly higher in infants with asphyxia than in a control group. The current study found a positive correlation between serum Troponin-T levels and total duration of respiratory support. Patients with high Troponin-T levels required more respiratory support. In addition, when the patients were divided into 3 groups according to their Troponin-T level,

the mortality rate was higher in the group with a high Troponin T level. These findings were considered to be in line with the literature.

Thrombocytopenia (platelet count <150,000/mL) is frequently encountered in asphyxia newborns. One reason for this is decreased oxygen delivery to the liver and bone marrow as a result of asphyxia, while another reason is the development of disseminated intravascular coagulation<sup>33</sup>. On the other hand, many studies<sup>34,35</sup> have reported that decreased thrombocyte levels may also develop due to the hypothermia treatment. Thrombocytopenia has been reported to be a significant cause of morbidity in asphytic neonates<sup>36</sup>. Therefore, the early identification of neonates at risk would be helpful in reducing morbidity with early intervention. Michniewicz et al<sup>13</sup> reported that thrombocytopenia was related to NE severity and morbidity. Similarly, Bala et al<sup>37</sup> showed a correlation between thrombocytopenia and NE severity. In addition to morbidity, it has also been shown in previous studies<sup>38-40</sup> that mortality is higher in newborns with thrombocytopenia. Consistent with the data in the literature, we showed lower

thrombocyte counts in the Sarnat Stage 3 group and a negative correlation between the thrombocyte values and the duration of intubation.

The serum lactate level increases in asphyctic neonates due to tissue hypoxia<sup>41</sup>. It has been reported that an elevation in serum lactate level is associated with the severity of NE<sup>13,42,43</sup>. Consistent with the literature, the serum lactate level was determined to be higher in the current study Sarnat Stage 3 cases compared to the Sarnat Stage 2 group.

Hepatic damage is known to develop secondary to hypoxia in perinatal asphyxia. It is also known that the serum ALT and AST values increase in patients diagnosed with NE because of the damage in hepatocytes<sup>44</sup>. The serum ALT level has been reported to increase 2-4-fold in infants diagnosed with severe NE compared to infants with moderate level NE, and ALT is more specific to hepatic damage than AST<sup>45</sup>. The increases in serum ALT and AST values seen in neonates diagnosed with NE have been shown to be associated with NE severity<sup>44,46-48</sup>. In the current study, the serum ALT and AST values of the Sarnat Stage 3 cases were seen to be higher than those of the Sarnat Stage 2 cases. Moreover, a significant positive correlation was determined between the serum ALT/AST ratio and the duration of intubation, the total duration of respiratory support, and the length of stay in the hospital. These results were found to be consistent with the literature.

### Limitations

The most important limitation of this study was that the echocardiography results of the patients were not included in the evaluations. Other limitations were the retrospective design, and that discharged patients were not followed up prospectively. The relatively high number of cases is the strength of this study.

### Conclusions

The Troponin-T level can be evaluated as a prognostic marker in patients with NE and receiving hypothermia treatment. Nevertheless, there is a need for further prospective studies with larger samples.

### Conflict of Interest

The authors declare that they have no conflict of interest.

### Funding

None.

### Informed Consent

The authors declare that informed permission forms were signed by the study participants before their medical information was used in the research.

### Authors' Contributions

Concept: G.Ü.,G.T., N. Ç.; Design: N.Ç., H.T.; Supervision: N.Ç.; Materials: G.Ü., G.T., N. Ç., H.T.; Data: G.Ü., G.T., N. Ç., H.T.; Analysis: G.Ü., N. Ç., H.T., G.T.; Literature search: G.Ü., N. Ç.; Writing: G.Ü., N. Ç.; Critical revision: G.Ü., N. Ç.

### Data Availability

The data used and analyzed during this research are available from Dr. N.Ç. upon reasonable request.

### Ethics Approval

Approval for the study was granted by the Ethics Committee of Sivas Cumhuriyet University Medical Faculty (Decision No: 2022-12/08, dated: 14.12.2022).

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