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Prognostic Value of Cardiac Biomarkers in Children with Acute Bronchiolitis

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Introduction: Determining the severity of acute bronchiolitis in children is important for the clinical management of the disease. Therefore, we aimed to reveal their prognostic importance by examining cardiac markers in our patients with acute bronchiolitis.
Materials and Methods: We conducted a single-center retrospective, observational study with children with acute bronchiolitis between 1 month and 2 years of age, between December 2020 and December 2021, who were covid-19 PCR test negative and had no covid-19 contact. We scanned demographic, clinical and laboratory parameters from medical records.
Results: A total of 45 (44% female) children with acute bronchiolitis, a median (IQR) age of 5 (5) months were included in the study. There were 7 (16%) mild bronchiolitis, 23 (51%) moderate and 15 (33%) severe bronchiolitis patients. The cutoff point of Nt-proBNP to be ≥1025 ng/L to predict severe bronchiolitis with a sensitivity of 71% and a specificity of 80 % at admission in children with acute bronchiolitis.
Conclusion: We think that the threshold value for Nt-proBNP in the study can be used to identify patients with severe bronchiolitis in the early period and to reduce mortality and morbidity by earlier intervention.

Keywords: Nt-proBNP, troponin-I, bronchiolitis, respiratory, children

Introduction

Acute bronchiolitis is the most common disease of the lower respiratory tract, mostly caused by viral infections, with inflammation of the bronchioles in infants younger than two years of age (1). Respiratory syncytial virus (RSV) is responsible for half of the patients, while adenovirus, human metapneumovirus, para-influenza, coronavirus and mycoplasma are the other factors (2, 3). According to WHO, it has been reported that there are 150 million acute bronchiolitis in the world annually, and 11-20 million cases require hospitalization (4).

Determining the severity is important for the clinical management of the disease (5). Treatment of mild bronchiolitis is symptomatic and outpatient follow-up of this patient group is possible. However, even mild cases can be followed up in hospitalization in cases such as nutritional deficiency and social indications. Moderate to severe bronchiolitis should be hospitalized and oxygenation provided (6). The

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patient's respiratory distress may increase 48-72 hours after the onset of symptoms. Significant respiratory distress, apnea, and respiratory acidosis may be observed. Other complications that can be seen other than respiratory failure include; cardiovascular involvement such as heart failure, myocarditis, pericardial effusion, inappropriate ADH syndrome and bronchiolitis obliterans in which obstructions are seen as a result of excessive formation of granulation tissue during the regeneration of bronchioles can be counted (7). Mortality between 0.2% and 7% has been reported worldwide, with varying rates according to regions (8). Patients should be followed closely in terms of complications and should be diagnosed at an early stage (9, 10).

When we searched the literature, we found that there are few studies on the importance of cardiac markers in patients with acute bronchiolitis. In our study, we aimed to reveal their prognostic importance by examining the demographic, hemogram, acute phase reactants and cardiac markers of pediatric patients with bronchiolitis. Thus, we think that mortality and morbidity can be reduced by using early diagnosis and treatment options.

Materials and Methods

Ethical Statement & Study Design

The research was designed as a retrospective single-center observational study. The present study was approved by the local ethics boards (2022/08-02) and complies with the provisions of the Declaration of Helsinki, which declares ethical principles to guide medical research. Children aged between 1 month and 2 years who were hospitalized in the pediatric ward and pediatric intensive care unit with the diagnosis of acute bronchiolitis in the 3rd step university hospital between December 2020 and 2021 were included in the study. These dates were concurrent with the COVID-19 pandemic period. In accordance with the hospital policy, patients who were positive for COVID-19 and patients with COVID-19 contact were followed in the isolated pediatric COVID-19 intensive care unit or in the pediatric covid-19 ward. Negative COVID-19 PCR test and no contact with COVID were included in the study.

Patients with congenital and acquired heart disease, immunodeficiency, hematological and oncological disorders, chronic pulmonary diseases such as bronchopulmonary dysplasia and cystic fibrosis were excluded. As the control group, it was planned to recruit healthy children of the same age group who applied to the pediatric cardiology outpatient clinic with a murmur without any disease. However, since it is a retrospective study, a sufficient number of healthy control groups whose hemogram and cardiac markers were taken from the same age group could not be obtained. Therefore, the study was conducted only with patients followed up with the diagnosis of acute bronchiolitis. Demographic characteristics and clinical findings of the patients and laboratory examinations at the time of admission were reviewed retrospectively from the records.

The Diagnosis of Acute Bronchiolitis

It was made according to the guidelines of the American Academy of Pediatrics (11). *Acute bronchiolitis severity* was graded as 5 points or less as mild, 6-10 moderate, and >10 points as severe bronchiolitis according to the bronchiolitis severity scoring system (12-14).

Measurement of Nt-proBNP

Serum proBNP were determined by using AQT90 FLEX (Radiometer Medical, Denmark) and the cutoff value was set at 133 ng/L.

Measurement of Troponin-I

Serum troponin-I levels were measured via a one-step enzyme immunoassay using a Roche Cobas 8000 automatic analyzer (with an analytical range of 0.01–0.02 µg/L).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 22 (IBM Corp., Armonk, NY, USA)

software package was used for statistical analysis. Study variables are presented as numbers (n) - percentages (%) or means ± standard deviations and median (inter quartile ranges). The normal distribution of variables was tested using the Kolmogorov-Smirnov test. Normally distributed parameters were evaluated by one-way analysis of variance or Student's t-test; non-normally distributed numerical variables were evaluated by the Kruskal-Wallis or Mann-Whitney U test. Chi-square or Fisher's test was used for comparison of categorical variables in the comparison of groups. The best cut-off point of Nt-proBNP was analyzed via the receiver operator characteristic (ROC) curve to predict severe bronchiolitis. P<0.05 was accepted as the limit value for significance.

Results

A total of 45 (44% female) children were followed up with the diagnosis of acute bronchiolitis. The median age (IQR) of the patients was 5 (5) months. The highest number of hospital admissions were in November (22%) and December (40%) in 2021. Demographical, clinical and laboratory characteristics are given in Table 1. When the patients were classified according to the severity of the disease, there were 7 (16%) children with mild bronchiolitis, 23 (51%) moderate and 15 (33%) children in the severe bronchiolitis. Clinical and laboratory characteristic were compared according to disease severity are given in table 2 and table 3. The number of patients treated in the intensive care unit was 12 (27%). 2 (4.4%) patients were intubated. 11 (24%) patients received high-flow nasal cannula oxygen (HFNC). Low-flow oxygen support was applied in other patients. When intubated patients, patients receiving high-flow oxygen, and patients receiving low-flow oxygen were compared with each other in terms of hospitalization time, no significant difference was found between them (median (IQR) 17.5, 10 (14), 8(3), respectively; p=0.062, Kruskal Wallis).

Table 1. Demographical and laboratory characteristics of children with acute bronchiolitis

Sex, n (%) - Female / Male	20 (44%) /25 (56%)
Age (month)	5 (5) *
Weight (kg)	6.2 (3.4) *
Length of hospital stay (day)	8 (4) *
Duration from onset of symptoms to admission (day)	3 (5) *
Vasoactive drug, n (%)	6 (%13)
Nt-proBNP (ng/L)	841 (1096) *
White blood cell (10^9/L)	13.427±4.444†
Neutrophil (10^9/L)	3.530 (5.34) *
Lymphocyte (10^9/L)	6.195±3.006 †
Monocyte (10^9/L)	1.267±0.547 †
Eosinophile (10^9/L)	0.170 (0.48) *
Hemoglobin (g/dL)	11±1.91 †
Platelet (10^9/L)	441 (137) *
Mean platelet volume (fL)	9.5±0.9 †
C- reactive protein (mg/L)	3 (7) *
Procalcitonin (µg/L)	0.12 (0.09) *

* median (IQR), † mean±SD

When all of the patients were evaluated, lymphocyte dominance was detected, and when evaluated according to the severity of the disease, neutrophils were found to be higher in patients with mild and severe bronchiolitis, while lymphocytes were found to be higher in patients with moderate bronchiolitis. Neutrophil -to-lymphocyte ratio (NLR) was similarly high in mild and severe severity and lower in moderate severity. There was no difference between the groups in other hemogram parameters except neutrophil and NLR ratio (Table 2). When all the patients were evaluated in general, the median (IQR) Nt-proBNP was 841 (1076) ng/L. As the disease severity increased, the Nt-proBNP also increased (Table 3). We found the best cutoff point of Nt-proBNP to be ≥1025 ng/L to predict severe bronchiolitis at admission in children with acute bronchiolitis. According to this cutoff point, Nt-proBNP has a sensitivity of 71% and a specificity of 80% for predicting severe

Table 2. Demographical and clinical characteristics compared according to severity of acute bronchiolitis

Variables	Mild *(n=7)*	Moderate *(n=23)*	Severe *(n=15)*	P value
Sex (female %)	57%	45%	46%	0.7
Age (month)	8 (10)	5 (4.25)	3 (9)	0.38
Weight (kg)	8.5 (12.5)	6.1 (1.7)	5.6 (3.7)	0.16
Height (cm)	75 (31)	61 (10)	59.5 (19)	0.12
Length of hospital stay (day)	6 (4)	8 (3)	13 (10)	0.012
Severity scoring	5 (0)	6 (0.25)	11 (3)	<0.001
Duration from onset of symptoms to admission (day)	6.5 (8.3)	3 (4)	3 (5)	0.72
Vasoactive drugs (dobutamine)	0	0	6 (% 40)	0.001

Statistics: Chi-square test and Kruskal Wallis test, median (IQR)

bronchiolitis (p=0.01) (Table 4). Troponin-I was positive in 5 (11.1%) children as 0.32 µg/L in one patient with severe bronchiolitis, 0.13 µg/L in one with moderate bronchiolitis, and 0.11 µg/L in three with moderate bronchiolitis.

Discussion

In the study, Nt-proBNP was shown that is important in the diagnosis and treatment of acute bronchiolitis, especially in the evaluation of the severity of bronchiolitis.

When we evaluated all patients with acute bronchiolitis, we found that the median (IQR) value of Nt-proBNP was 841 (1076) ng/L, and this value was above the population average (15). When the disease was evaluated according to the severity, it was found that the Nt-proBNP increased as the disease got worse. In addition, a cutoff value was given for Nt-proBNP in the study to predict severe bronchiolitis. Nt-proBNP is mainly released from left ventricular myocytes by hypoxia, ischemia, Mechanical stress and neurohumoral factors. Nt-proBNP causes natriuresis, diuresis and vasodilation (16-18). It was positive correlated to pulmonary vascular resistance, right ventricular diameter, and right atrial pressure. the survival rate was increased when Nt-proBNP decreased with treatment (19). In a few studies, Nt-proBNP was stated that demonstrated the severity of the disease in the early period in children with acute bronchiolitis (20, 21). In a study, Nt-proBNP was reported that associated with the need for respiratory support at presentation (22). In our study, the Nt-proBNP of 1025 ng/L and above at the time of admission was shown that predictive of severe bronchiolitis with 80% specificity and 71% sensitivity.

In the study, troponin-I was positive in four children, one of whom was in the severe bronchiolitis. It is a heart-specific enzyme that is sensitive in demonstrating myocardial damage (23). Although they show high specificity in predicting myocarditis in children, it has been reported that they are not associated with the degree of myocardial dysfunction (24, 25). Troponin-I, which is sensitive to show even minimal myocardial damage, has been reported that elevated in some patients with acute bronchiolitis (26). However, in a meta-analysis by Gonzalez et al. and in a separate study of 40 children with acute bronchiolitis, they reported that the disease did not predict severity in children with acute bronchiolitis (10, 20). In our study, the fact that troponin elevation was observed mostly in moderately ill patients supports this view. 27% of our patients were followed up in the intensive care unit. 17% of patients with acute bronchiolitis has been reported that mostly require hospitalization, and approximately 5.4% of them are connected to mechanical ventilator (27). In a study, 20% of

Table 3. Laboratory findings compared according to severity of acute bronchiolitis

Variables	Mild *(n=7)*	Moderate *(n=23)*	Severe *(n=15)*	P value
White blood cell (10^9 /L)	15.930 (8.760)	10.700 (6.070)	14.070 (8.940)	0.16
Neutrophil (10^9 /L)	7.230 (11.000)	3.030 (3.400)	6.950 (5.300)	0.04
Lymphocyte (10^9 /L)	2.490 (7.120)	5.990 (3.400)	5.730 (3.630)	0.63
Monocyte (10^9 /L)	1.430 (1.910)	1.270 (0.870)	1.370 (0.910)	0.9
Eosinophile (10^9 /L)	0.090 (0.160)	0.170 (0.550)	0.150 (0.450)	0.27
Red blood cell (10^{12}/L	4.4 (1.6)	4.1 (0.7)	4.2 (1.6)	0.2
Hemoglobin (g/L)	10.9 (2.3)	10.7 (1.7)	10.7 (2.2)	0.8
Hematocrit (%)	34 (6)	32.8 (6.1)	33.1 (6.25)	0.49
Mean corpuscular volume (fL)	77.9 (14.8)	79.2 (16.9)	82.7 (16.7)	0.18
Red blood cell distribution (%)	13.2 (3.2)	14.4 (3.5)	13.8 (1.88)	0.9
Platelet (10^9/L)	474000 (144500)	430000 (124000)	369500 (143750)	0.48
Mean platelet volume (fL)	9.4 (1.7)	9.5 (1.4)	10.05 (1.4)	0.43
Neutrophil to Lymphocyte (NLR)	1.3 (4.29)	0.45 (0.35)	0.9 (2.9)	0.019
C-reactive protein (mg/L)	6 (7)	3(3)	6 (16)	0.12
Procalcitonin (µg/L)	0.08 (1.53)	0.11 (0.08)	0.15 (0.38)	0.15
Nt-proBNP (ng/L)	220 (391)	784 (705)	1665 (2363)	0.008
Creatine kinase (u/l)	93 (59)	75 (50)	113.5 (77.75)	0.09
Creatine kinase-MB (ug/l)	3.85 (3.18)	4.4 (2.4)	5.65 (6.75)	0.17

Statistics: Kruskal wallis test, median (IQR)

Table 4. Determination of Nt-proBNP cut-off point to predict severe bronchiolitis in children with acute bronchiolitis

Variable	Cut-off	AUC	Sensitivity	Specificity	95% CI	P value
Nt-proBNP (ng/L)	1025	0.751	0.71	0.80	0.57-0.94	0.01

the patients hospitalized for bronchiolitis was reported that necessary intensive care, and 3% were connected to a mechanical ventilator (28). Approximately 4% were intubated and followed up on a mechanical ventilator. While 24% of our patients were treated HFNC, 71% of them were administered low-flow oxygen. HFNC therapy is widely used among pediatricians in patients with respiratory distress (29). In the treatment of bronchiolitis, HFNC is highly utilized (30). In a prospective study conducted with 87 children, Esik et al. reported HFNC decreased respiratory rate and respiratory severity (31). In a controlled study by Franklin et al., it was reported that treatment failure was lower in those treated with high flow oxygen than those treated with low flow oxygen. However, in the same study, no difference was found between the groups in terms of length of hospital stay, duration of oxygen therapy, and need for intensive care (32). In another randomized controlled study, no difference was found between those who received high-flow oxygen and those who received low-flow oxygen in terms of length of hospital stay, duration of oxygen therapy, and need for intensive care (30). In our study, although there was no statistically significant difference in terms of hospital stay between those who were intubated, those who received high flow oxygen, and those who received low flow oxygen, the length of stay was longer in intubated cases.

Vasoactive medication was required in 6 of patients followed in the intensive care, and dobutamine was administered to the patients. Dobutamine increases cardiac contraction, dilates peripheral vessels in the lung, thereby reducing pulmonary resistance and correcting

pulmonary blood flow and ventilation-perfusion mismatch. In addition, a study suggested that dobutamine increases apoptosis in neutrophils (33, 34). Therefore, it may have a positive effect on lungs by reducing pulmonary inflammation. Our patients were also clinically relieved after dobutamine administration and were discharged with recovery. In the study, no statistical difference was found between the severity of acute bronchiolitis and complete blood count parameters, except for neutrophils. Neutrophil count was also found to be high in mild and severe severity and lower in moderate severity. The reason for this can be explained by the delayed admission of mild cases to the hospital and the increase in inflammation as the disease duration increases. It has been reported neutrophil dominance is observed especially in bronchiolitis caused by RSV and 80% of cellular infiltrate is formed in severe bronchiolitis (35). Therefore, neutrophil elevation can be explained in our cases with severe bronchiolitis.

The main limitations of the study are that it was conducted in a single centre, with a small number of patients, and most importantly, its retrospective design. In addition, the absence of a control group is another important limitation.

Conclusion

Nt-proBNP was an important marker in the diagnosis and follow-up of acute bronchiolitis. In addition, Nt-proBNP cutoff to predict severe bronchiolitis was determined. Positive troponin-I value was determined that no indicated the severity of the disease. In addition, it is beneficial to use dobutamine when there is a need for vasoactive drugs in patients who need intensive care. Our study will guide clinicians following acute bronchiolitis in terms of diagnosis and treatment, and by recognizing patients with severe bronchiolitis in the early period, necessary treatment and precautions can be taken, and thus mortality and morbidity can be reduced.

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