

## Association of NT-proBNP with clinical outcomes in children with systemic inflammatory response syndrome

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### ABSTRACT

N-terminal pro-brain type natriuretic peptide (NT-proBNP) has been reported to have an association with increased morbidity and mortality in adults with septic shock. The relationship between NT-proBNP levels and morbidity/mortality in children with systemic inflammatory response syndrome (SIRS) has not been studied. This was a retrospective study. The inclusion criteria were children (< 18 years of age) who met the SIRS criteria and had NT-proBNP obtained between 2011 and 2017. Patients with final primary diagnoses related to cardiac disease were excluded. Patients were divided into 2 groups based on the value of NT-proBNP levels. Our cohort consisted of 44 patients after screening 4004 patients. Primary diagnoses were bacterial infection ( $n = 35$ , 80%), viral infection ( $n = 6$ , 14%), and Kawasaki disease ( $n = 3$ , 7%). Between elevated ( $n = 26$ ) and non-elevated ( $n = 18$ ) groups, there was no difference in age groups, gender, race, or final diagnoses. There were 5 deaths (11%). Children in the elevated group were more likely to require intensive care unit admission (odds ratio 20.0), mechanical ventilation (5.0), and inotropic support (9.4). Using receiver operator characteristic curve, the optimal cut-off values of NT-proBNP were 3034 pg/mL for inotropic support and mechanical ventilator use, 818 pg/mL for ICU admission, and 29,988 pg/mL for mortality. NT-proBNP levels were associated with increased morbidity in children with SIRS.

### 1. Introduction

Brain-type natriuretic peptide (BNP) is a cardiac biomarker that has many important properties in the body. BNP induces natriuresis and vasodilation, inhibits the renin-angiotensin-aldosterone system, and suppresses hypertrophy and fibrosis. The prohormone proBNP is secreted by cardiomyocytes in response to various stressors such as stretching of the myocardium by volume overload. ProBNP is then cleaved into the biologically active BNP and non-biologically active N-terminal pro-brain type natriuretic peptide (NT-proBNP) by the enzymes furin and corin. Unlike BNP, NT-proBNP is more stable in the blood as it is not actively degraded by enzymes [1].

Both BNP and NT-proBNP have been shown to be clinically useful in diagnosing and guiding treatment in adults with congestive heart failure. Higher levels have been associated with poorer prognosis in patients with congestive heart failure (CHF). In addition, NT-proBNP has been used to differentiate acute heart failure from pulmonary disease in the emergency department [2,3]. In regards to children, BNP and NT-proBNP have mostly been used to monitor heart failure

symptoms in those with congenital heart disease. Sugimoto et al. found that increasing levels of BNP and NT-proBNP correlated with severity of CHF in children. Recent modifications to the Ross classification for heart failure in children have included NT-proBNP levels for this reason [4,5].

BNP and NT-proBNP levels may be useful in clinical situations other than CHF. Law et al. investigated the use of BNP levels in diagnosing significant structural or functional cardiovascular disease in children [6]. In addition, elevated BNP and NT-proBNP levels have been associated with increased morbidity and mortality in adults that present with septic shock [7]. Samransamruajkit et al. also found a higher mortality rate among pediatric patients with elevated NT-proBNP levels that presented with severe sepsis and septic shock [8].

Systemic inflammatory response syndrome (SIRS) is a spectrum of symptoms including fever/hypothermia, tachycardia, tachypnea, and abnormal white blood cell count that relates to a body's inflammatory response. Various pathologic processes involving systemic inflammation may result in SIRS. Patients with SIRS often manifest with signs of cardiac dysfunction and perfusion abnormalities [9,10]. The utility of

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**Table 1**  
Systemic inflammatory response syndrome (SIRS) criteria (A) and scale (B).

(A) SIRS criteria <sup>a</sup>					
Age group	Primary criteria		Additional criteria		
	Temperature (degree C)	Leukocytes ( $\times 10^3/\text{mm}^3$ )	Heart rate (beats/min)	Respiratory rate (breaths/min)	Systolic Blood Pressure (mmHg)
0 days to 1 week	< 36.0	> 34	< 100	> 60	< 59
> 1 week to 1 month	> 38.0	< 5	> 180	> 50	< 75
> 1 month to < 2 year	< 36.0	> 19.5	< 100	> 50	< 75
2 to < 6 years	> 38.0	< 5	> 180	> 35	< 75
6 to < 13 years	> 36.0	> 17.5	> 180	> 30	< 75
13 to < 18 years	< 36.0	< 6	> 140	> 20	< 83
	> 38.0	> 15.5	> 130	> 20	< 83
	< 36.0	< 4.5	> 130	> 20	< 83
	> 38.0	> 13.5	> 110	> 20	< 90
	< 36.0	< 4.5	> 110	> 20	< 90
	> 38.0	> 11			

(B) SIRS scale			
SIRS scale	SIRS criteria	Impaired perfusion (impaired conscious state, oliguria, hypoxemia, or lactic acidosis)	Shock
SIRS 1	+	–	–
SIRS 2	+	+	–
SIRS 3	+	+	+

<sup>a</sup> Patients meet SIRS criteria if they have abnormal temperature or abnormal leukocyte count and 1 additional criterion is met.

NT-proBNP has not been studied as a prognostic biomarker in children with SIRS.

The objective of this study was to evaluate the impact of elevated NT-proBNP levels on clinical outcomes in pediatric patients that met criteria for SIRS. The hypothesis was that elevated NT-proBNP levels are associated with increased mortality and morbidity in children with SIRS.

## 2. Methods

The electronic medical record at the Children's Hospital of Michigan was retrospectively reviewed for all patients admitted between January 2011 and October 2017. Subsequently, ICD-9 and ICD-10 codes were used to generate a list of those with a diagnosis of infection (Appendix). Children were included in the study if they were under the age of 18 years at time of admission, presented for evaluation of a suspected infection, met SIRS criteria (Table 1A), and had a NT-proBNP level drawn during their hospital stay. Patients were excluded if they had known pre-existing congenital heart disease, pre-existing acquired heart disease, or had a final diagnosis that was primarily related to cardiac disease (pericarditis, myocarditis, or dilated cardiomyopathy).

The electronic medical record was used to collect demographics, diagnoses, length of stay, need for the intensive care unit (ICU), mortality at time of discharge, types of test ordered, imaging modalities utilized, laboratory results, treatments, and duration of treatments. If multiple NT-proBNP levels were drawn, the first level drawn during their admission was used. Sugimoto et al. found various cut-off points for NT-proBNP levels via receiver operating characteristic analysis that corresponded to no, mild, moderate, and severe CHF symptoms. These cut-off values were later incorporated into the modified Ross classification for heart failure in children. Therefore, the value of NT-proBNP was classified into two groups based on these previous heart failure reports [4,5]. Group 1 had normal or mildly elevated levels: < 1700 pg/mL for young children (< 3 years of age) and < 1500 pg/mL for

older children and adolescents (3 to < 18 years of age). Group 2 had moderately or severely elevated levels ( $\geq 1700$  pg/mL for young children and  $\geq 1500$  pg/mL for older children and adolescents). The SIRS scale was calculated (Table 1B) [11]. SIRS 1 was defined as meeting SIRS criteria without impaired perfusion or shock. SIRS 2 was defined as SIRS 1 and impaired perfusion without shock. SIRS 3 was defined as SIRS 2 and shock. Impaired perfusion was defined as 1 of the following: impaired conscious state, oliguria, hypoxemia, or lactic acidosis. Estimated glomerular filtration rate (eGFR) was calculated by bedside Schwartz equation:  $\text{eGFR (mL/min/1.73 m}^2) = 0.413 \times (\text{height in cm/serum creatinine})$  [12]. All electrocardiography (ECG) and echocardiography studies were reviewed by a single examiner (EM). Fractional shortening was calculated based on measurements of left ventricular dimensions in the parasternal short-axis view at the level of the papillary muscles via M-mode tracings ( $\text{FS} = (\text{LVEDD} - \text{LVESD}) / \text{LVEDD} \times 100$ ). Whereas, ejection fraction was calculated via the simplified Quinones equation ( $\text{EF} = (\text{LVEDD}^2 - \text{LVESD}^2) / \text{LVEDD}^2 \times 100$ ). The study was approved by the institutional review board at Wayne State University and by the Detroit Medical Center.

Data was expressed as median (range) and frequency (percentage) based on continuous and nominal variables, respectively. Chi-square and non-parametric tests were used to compare the data between 2 groups based on the type of variables and data distribution. The ROC curve was used to analyze the optimal cut-off value of biomarkers for morbidity (inotropic support, mechanical ventilator use, ICU admission) and mortality. SPSS version 25 (IBM Corp, Armonk, NY) was used to perform statistical analysis. A  $p < 0.05$  was considered statistically significant.

## 3. Results

Among a total of 4004 patients screened, 174 met our inclusion criteria. Of those that met inclusion criteria, 130 patients were excluded for underlying conditions of congenital heart disease ( $n = 39$ ), acquired heart disease ( $n = 24$ ), pulmonary hypertension ( $n = 28$ ), final/primary diagnosis of pericarditis ( $n = 8$ ), myocarditis ( $n = 25$ ), dilated cardiomyopathy ( $n = 4$ ), or incomplete medical record ( $n = 2$ ). As a result, our study cohort consisted of 44 patients (Fig. 1).

### 3.1. Patient characteristics

In this cohort, 10 patients were infants (28 days to < 1 year of age), 19 were children (1 to < 12 years of age), and 15 were adolescents (12 to < 18 years of age). Males comprised of 55% of the study population. Half of patients had no significant past medical history. Past medical problems included cancer ( $n = 6$ ), asthma ( $n = 4$ ), systemic lupus erythematosus ( $n = 4$ ), sickle cell disease ( $n = 3$ ), and renal disease ( $n = 3$ ). Median weight was 17.4 kg (range: 4.6 to 140 kg) and median height was 101 cm (27.5 to 171 cm). The chief complaint was fever in 24 patients followed by respiratory complaints in 9 patients. Cardiac complaints were rare, occurring in only 2 patients. All patients met the SIRS criteria.

Final diagnoses (Table 2) were related to bacterial infection ( $n = 35$ , 80%), viral infection ( $n = 6$ , 13%), and Kawasaki disease ( $n = 3$ , 7%). Among the patients with a diagnosis of bacterial infection, bacterial cultures were positive in twenty patients. Viral infection was confirmed by respiratory viral PCR panel in 5 patients. In the remainder of patients without positive confirmatory tests, bacterial or viral infection was presumed based on clinical symptoms, radiographic imaging, and laboratory results. The median length of hospital stay was 9 days (1 to 41 days). Inotropic medications were used in twenty patients with a median duration of 5 days (1 to 16 days). A total of sixteen patients required mechanical ventilation with a median duration of 6 days (3 to 25 days). All of the patients received antimicrobial therapy except for 1 patient who had the diagnosis of viral bronchiolitis. The median duration of antimicrobial therapy was 7 days (2 to 25 days).

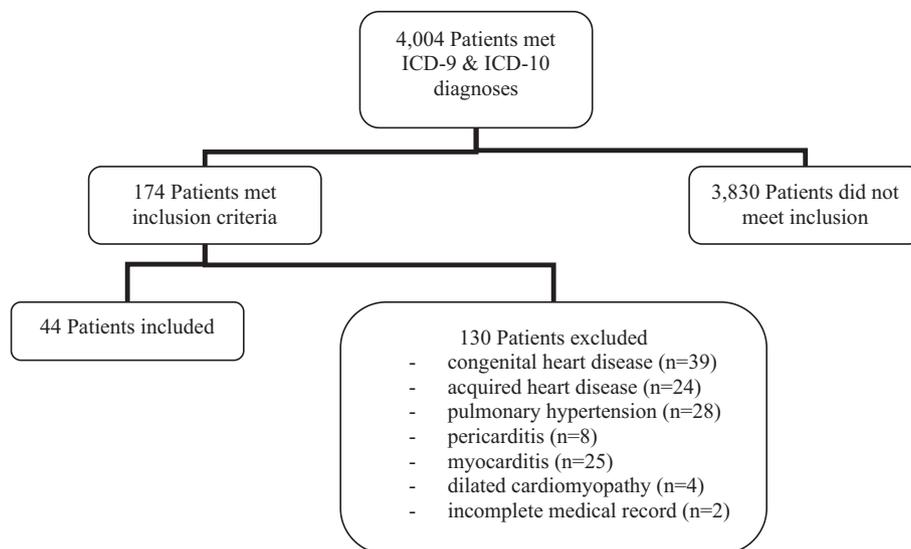


Fig. 1. Patient selection tree.

**Table 2**  
Demographics, vital signs, final diagnosis and systemic inflammatory response syndrome (SIRS) scale.

Variables	Total (n = 44)	Group 1 (n = 18)	Group 2 (n = 26)	p value
<b>Age</b>				
Neonate (0 to < 28 days)	0 (0%)	0 (0%)	0 (0%)	NS
Infant (28 days to < 1 years)	11 (25%)	5 (28%)	6 (23%)	
Child (1 to < 12 years)	21 (48%)	10 (55%)	11 (42%)	
Adolescent (12 to < 18 years)	12 (27%)	3 (17%)	9 (35%)	
<b>Sex</b>				
Male	24 (55%)	7 (39%)	17 (65%)	NS
Female	20 (45%)	11 (61%)	9 (35%)	
<b>Race</b>				
Caucasian	11 (25%)	6 (33%)	5 (19%)	NS
African American	24 (54%)	9 (50%)	15 (58%)	
Hispanic	3 (7%)	2 (11%)	1 (4%)	
Unknown	6 (14%)	1 (6%)	5 (19%)	
Weight (kg)	17.4 (4.6–140)	15.6 (6.3–140)	17.6 (4.6–132)	NS
Height (cm)	101 (27.5–171)	90.5 (27.5–165)	103 (48–171)	NS
<b>Chief complaint</b>				
Fever	27 (61%)	10 (55%)	17 (66%)	NS
Respiratory	9 (20%)	5 (28%)	4 (15%)	
Cardiac	2 (5%)	2 (11%)	0 (0%)	
Other	6 (14%)	1 (6%)	5 (19%)	
Temperature (°C)	39.1 (35.8–41)	39.0 (36.6–40.6)	39.3 (35.8–41)	NS
Heart rate (beats/minute)	151 (64–212)	150 (109–200)	151 (64–212)	NS
Systolic blood pressure (mmHg)	108 (77–147)	113 (83–147)	100 (77–136)	< 0.05
Diastolic blood pressure (mmHg)	57 (20–110)	64 (51–89)	55 (20–110)	< 0.05
Respiratory rate (/minute)	38 (18–69)	38 (18–68)	38 (20–69)	NS
Oxygen requirement	8 (18%)	2 (11%)	6 (23%)	NS
<b>Final Diagnosis</b>				
Bacterial infection	35 (80%)	13 (72%)	22 (84%)	NS
- Blood stream infection	12	1	11	
- Pneumonia	6	3	3	
- Ear, nose, throat infection	2	1	1	
- Genitourinary infection	3	1	2	
- Skin/soft tissue infection	3	3	0	
- Gastrointestinal infection	1	0	1	
- Cerebral spinal fluid	1	0	1	
- Culture negative	7	4	3	
Viral infection	6 (13%)	5 (28%)	1 (4%)	
Kawasaki disease	3 (7%)	0 (0%)	3 (12%)	
<b>SIRS scale</b>				
- 1	19 (43%)	13 (72%)	6 (23%)	< 0.05
- 2	9 (21%)	3 (17%)	6 (23%)	
- 3	16 (36%)	2 (11%)	14 (54%)	

Data are expressed as median (range) or frequency (percentage) based on variable type.

There were 5 patients that died during the study period. On SIRS scale, sixteen patients (36%) had SIRS 3, whereas 9 (21%) had SIRS 2 and nineteen (43%) had SIRS 1. The median value of NT-proBNP was 1894 pg/mL.

### 3.2. NT-proBNP and subsequent cardiac tests

Tachycardia ( $n = 25$ , 57%) was the primary indication for NT-proBNP levels to be drawn followed by refractory hypotension ( $n = 16$ , 36%). Other reasons NT-proBNP levels were ordered included cardiomegaly on chest X-ray, metabolic acidosis on blood gas analysis, and chest pain. NT-proBNP levels were normal ( $< 450$  pg/mL in children  $< 3$  years of age or  $< 300$  pg/mL in children 3 years to  $< 18$  years of age) in ten patients (23%), mildly elevated (450 to  $< 1700$  pg/mL in children  $< 3$  years of age or 300 to 1500 pg/mL in children 3 years to  $< 18$  years of age) in 8 patients (18%), and moderately to severely elevated ( $\geq 1700$  pg/mL in children  $< 3$  years of age or  $\geq 1500$  pg/mL in children 3 years to  $< 18$  years of age) in twenty six patients (59%) [4]. Among the thirty four patients with an abnormal NT-proBNP value, the majority underwent additional cardiac evaluation including ECG ( $n = 27$ , 80%), echocardiogram ( $n = 30$ , 88%) and cardiology consultation ( $n = 16$ , 47%). Among the 10 patients with normal NT-proBNP, 8 patients (80%) had an ECG, 7 patients (70%) had an echocardiogram, and 1 patient (10%) had a cardiology consultation.

ECG findings were normal in 74% of patients. Abnormalities on ECG include ventricular hypertrophy (9%), ST segment changes (3%), T-wave abnormalities (11%), and atrial fibrillation (3%). Left ventricular systolic function on echocardiogram was quantitatively normal in twenty six patients (70%), mildly decreased in 4 patients (10%), moderately decreased in 2 patients (5%), and severely decreased in 2 patients (5%). Other findings on echocardiogram included chamber dilation (14%), significant valvular insufficiency (8%), pericardial effusion (14%), and thrombus formation (3%).

### 3.3. Comparison between groups

Group 1 was composed of 5 infants (28%), 10 children (55%), and 3 adolescents (17%) compared to 6 infants (23%), 11 children (42%), and 9 adolescents (35%) group 2 (Table 2). There was no significant difference in age groups, sex, race/ethnicity, past medical history, weight, or height between the two groups. Fever at time of admission was common among both groups. Both systolic and diastolic blood pressures were lower in group 2, whereas there was no difference in heart rate, respiratory rate, or oxygen requirement. Group 2 was more likely to have higher SIRS scale scores of 2 or 3 ( $p < 0.05$ ).

There was a median NT-proBNP value of 7500 pg/mL in group 2 and 316 pg/mL in group 1 (Table 3). The majority (77%) of NT-proBNP

levels were drawn within 2 days of admission. Group 2 had higher values of C-reactive protein (CRP), serum blood urea nitrogen (BUN), and serum creatinine, and had lower values of hemoglobin, hematocrit, and eGFR ( $p < 0.05$ ). Remaining laboratory tests including white blood cell count, sodium, transaminases, and bicarbonate were similar among both groups. Blood cultures were positive in 3 patients (17%) in group 1 compared to 11 patients (42%) in group 2.

Majority of ECG tests performed were normal in both groups (Table 4). Echocardiogram and cardiology consultation was obtained more frequently in group 2 ( $p < 0.05$ ). Qualitatively, reduced left ventricular systolic function was observed more in group 2 ( $p < 0.05$ ). Quantitatively, group 2 had a lower ejection fraction (59.3 vs. 69.0%;  $p < 0.05$ ) and shortening fraction (30.3 vs. 36.7%;  $p < 0.05$ ).

Table 5 shows the morbidity and mortality between the two groups. Children in group 2 were more likely to require intensive care unit admission (odds ratio 20.0 [95% confidence interval: 2.2 to 181]), mechanical ventilation (OR 5.0 [1.2 to 21.5]), and inotropic support (OR 9.4 [2.2 to 41.5]). One patient died in group 1 and four patients died in group 2.

### 3.4. Mortality cases

One patient in group 1 died. She was a 16-year-old female with acute encephalitis secondary to enterovirus infection. She ultimately expired after acute decompensation despite maximal resuscitation efforts. Her NT-proBNP was 35 pg/mL.

Four patients in group 2 died. The first patient was a 17-year-old male with history medulloblastoma who had pancytopenia and profound hypotension due to *Streptococcal pneumoniae* sepsis. The second case was an 18-month-old previously healthy male with *Streptococcal pneumoniae* meningitis. The third case was an 11-year-old male with acute lymphoblastic leukemia relapse who presented with fever, neutropenia, and profound hypotension secondary to *Escherichia coli* sepsis. The final case was a previously healthy 6-week-old male with fulminant sepsis secondary to *Citrobacter*. He died of brain death after a trial of extracorporeal membrane oxygenation. For each mortality case in group 2, the NT-proBNP level was  $> 35,000$  pg/mL.

### 3.5. Receiver operator characteristic curve analysis

Using ROC curve analysis, the optimal cut-off values of NT-proBNP were 3034 pg/mL for inotropic support and mechanical ventilator use, 818 pg/mL for ICU admission, and 29,988 pg/mL for mortality (Table 6A, Fig. 2). In the analysis of biomarkers, the area under the curve values were compared (Table 6B). The SIRS scale and NT-proBNP were the best predictors for morbidity and mortality.

**Table 3**  
Laboratory test results.

Variables	Total (n = 44)	Group 1 (n = 18)	Group 2 (n = 26)	p value
NT-proBNP (pg/mL)	1894 (35– > 35,000)	316 (35–1451)	7500 (1595– > 35,000)	< 0.05
White blood cell ( $\times 10^3/\text{mm}^3$ )	11.8 (0.1–39.4)	14.9 (0.2–31.7)	8.4 (0.1–39.4)	
Bands (%)	1 (0–55)	1 (0–4)	6 (0–55)	NS
Neutrophil (%)	66 (10–93)	67 (10–93)	66 (13–92)	
Lymphocyte (%)	17 (2–75)	24 (3–75)	15 (2–54)	
Hemoglobin (gm/dL)	10.6 (5.9–14.2)	12 (7.9–14.2)	10.2 (5.9–14.1)	< 0.05
Hematocrit (%)	31.5 (13.7–41.7)	34.2 (23.7–39.8)	30 (13.7–41.7)	< 0.05
Platelet count ( $\times 10^3/\text{mm}^3$ )	246 (11–587)	261 (21–501)	239 (11–587)	NS
C-reactive protein (mg/L)	153 (3.73– > 180)	70 (3.73– > 180)	208 (29– > 180)	< 0.05
Sodium (mmol/L)	135 (123–149)	136 (132–141)	133 (123–149)	NS
Alanine aminotransferase (units/L)	32 (< 11–180)	22 (17–89)	35 (< 11–180)	NS
Aspartate aminotransferase (units/L)	36 (16–355)	29 (16–171)	42 (17–355)	NS
Bicarbonate (mmol/L)	21 (11–39)	21 (17–30)	21 (11–39)	NS
Blood urea nitrogen (mg/dL)	11 (3–70)	9 (3–16)	15 (6–70)	< 0.05
Creatinine (mg/dL)	0.6 (0.18–1.87)	0.5 (0.18–0.7)	0.8 (0.23–1.87)	< 0.05
Estimated glomerular filtration rate (mL/min/1.73 m <sup>2</sup> )	79 (12–196)	95 (55–161)	67 (12–196)	< 0.05

**Table 4**  
List of additional tests.

Test	Variables	Group 1 (n = 18)	Group 2 (n = 26)	p value	
Chest X-ray	Ordered	18/18 (100%)	26/26 (100%)	NS	
	Normal	4 (22%)	8 (31%)	NS	
	Abnormal	14 (78%)	18 (69%)		
	- Small airway disease	8	4		
	- Pleural effusion	2	1		
Electrocardiogram	Ordered	13/18 (72%)	22/26 (85%)	NS	
	Normal	10 (77%)	16 (73%)	NS	
	Abnormal	3 (23%)	6 (27%)		
	- Hypertrophy	2	1		
	- ST segment abnormality	0	1		
Echocardiogram	Ordered	12/18 (67%)	25/26 (96%)	< 0.05	
	Normal	10 (84%)	10 (40%)	< 0.05	
	Abnormal	2 (16%)	15 (60%)		
	- Pericardial effusion	1	4		
	- Reduced function	1	8		
	- Thrombus/vegetation	0	1		
	- Chamber dilation	0	5		
	- Valve insufficiency	0	3		
	Quantitative function assessment <sup>a</sup>				
	Ejection fraction	69% (51.3 to 73.7)	59.3% (27.3 to 75)	< 0.05	
	- Normal ( $\geq 52\%$ )	9	17		
	- Mildly reduced (41–51%)	1	3		
	- Moderately reduced (30–40%)	0	4		
- Severely reduced (< 30%)	0	1			
Shortening fraction	36.7% (26.3 to 43)	30.3% (12.8 to 43)	< 0.05		
- Normal (25–43%)	10	17			
- Mildly reduced (20–24%)	0	4			
- Moderately reduced (15–19%)	0	2			
- Severely reduced ( $\leq 14\%$ )	0	2			
Cardiology consultation		2 (11%)	15 (58%)	< 0.05	

<sup>a</sup> Cut-off values for function based on current American Society of Echocardiography guidelines [15].

**Table 5**  
Comparison of morbidity and mortality between elevated and non-elevated NT-proBNP groups.

	Group 1 (n = 18)	Group 2 (n = 26)	Odds ratio	95% confidence interval	p value
Inotropic support	3 (17%)	17 (65%)	9.4	2.2 to 41.5	< 0.05
Mechanical ventilation use	3 (17%)	13 (50%)	5.0	1.2 to 21.5	< 0.05
ICU admission	10 (55%)	25 (96%)	20.0	2.2 to 181	< 0.05
Mortality at Discharge	1 (6%)	4 (15%)			NS

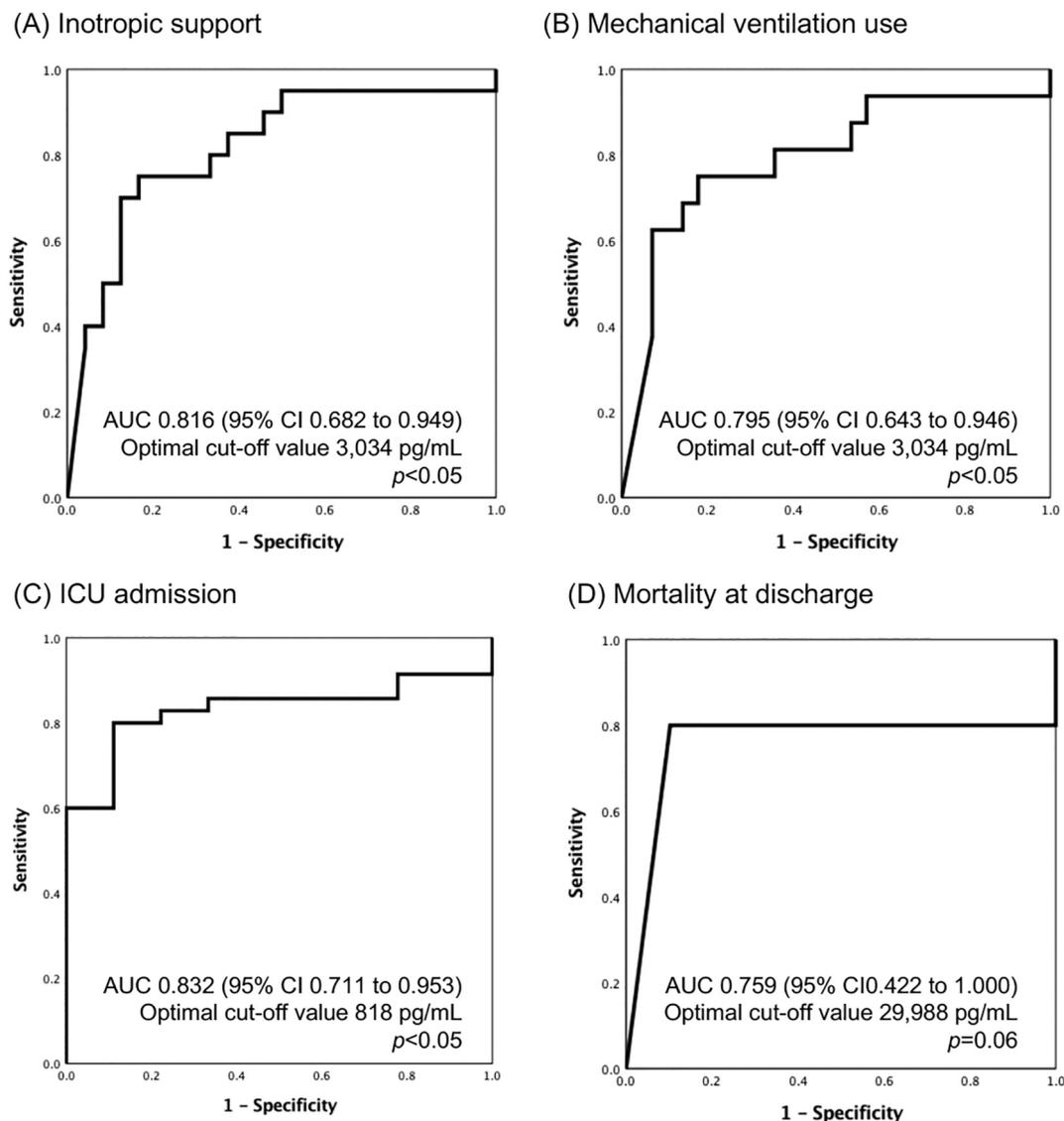
**Table 6**  
Receiver operator characteristic curve analysis of biomarkers for morbidity and mortality in children with systemic inflammatory response syndrome.

(A) ROC curve analysis of NT-proBNP for morbidity and mortality					
	Area under the curve (95% CI)	p value	Optimal cut-off	Sensitivity	Specificity
Inotropic support	0.816 (0.682 to 0.949)	< 0.05	3034	0.750	0.875
Mechanical ventilator use	0.795 (0.643 to 0.946)	< 0.05	3034	0.750	0.821
ICU admission	0.832 (0.711 to 0.953)	< 0.05	818	0.800	0.889
Mortality at discharge	0.759 (0.422 to 1.000)	0.06	29,988	0.800	0.897

(B) Comparison of area under the curve values in the ROC curve analysis of biomarkers for morbidity and mortality				
	Inotropic support	Mechanical ventilation use	ICU admission	Mortality at discharge
SIRS scale	0.953*	0.801*	0.768*	0.859*
NT-proBNP	0.816*	0.795*	0.832*	0.759
Estimated glomerular filtration rate	0.750*	0.725*	0.606	0.744
Creatinine	0.706	0.633	0.705	0.869*
Hematocrit	0.688	0.651	0.624	0.592
Blood urea nitrogen	0.657	0.598	0.652	0.713
Hemoglobin	0.652	0.604	0.610	0.551
CRP	0.510	0.569	0.542	0.964

\*  $p < 0.05$ .



**Fig. 2.** Receiver operating characteristic curves for NT-proBNP level in predicting morbidity and mortality in children with systemic inflammatory response syndrome. NT-proBNP predicted (A) inotropic support, (B) mechanical ventilation use, (C) intensive care unit (ICU) admission, (D) mortality at discharge. AUC, area under the curve; CI, confidence interval.

#### 4. Discussion

In this study, patients that had moderately to severely elevated NT-proBNP levels had higher levels of CRP, serum BUN, and serum creatinine along with lower hemoglobin and hematocrit levels. They also had lower left ventricular systolic function on echocardiogram. These findings likely represent a higher degree of illness among patients with moderately to severely elevated NT-proBNP levels. Patients with moderately to severely elevated NT-proBNP levels were more likely to require ICU care, mechanical ventilation, and inotropic support, and extremely elevated NT-proBNP levels were associated with increased morbidity in children with SIRS. In this cohort, there was an 11.4% mortality rate (5 of 44 subjects), with the majority (4 of 5) of cases having severely elevated NT-proBNP levels of > 35,000 pg/mL. This finding is consistent with prior studies showing higher NT-proBNP levels in non-survivors compared to survivors with sepsis [7,8].

The mechanism for elevation of NT-proBNP in children with SIRS is not clear. Varpula et al. speculated that resuscitation efforts such as increased volume load from fluid boluses, use of vasoactive medications, and positive pressure ventilation may result in myocardial stress and, therefore, result in the production of NT-proBNP [7]. However,

Chun-Wang Lin et al. found that there was no significant difference in NT-proBNP levels between patients that received large amount of volume versus those that received smaller amount of volume for fluid resuscitation [13]. Another theory is that the inflammatory response to infection could result in elevation of NT-proBNP levels. A previous study showed that inflammatory cytokines such as interleukin-1 $\beta$  and tumor necrosis factor  $\alpha$  caused BNP to be secreted by cardiomyocytes [14].

A biomarker that can be used as a prognostic maker to estimate the severity of illness is particularly advantageous for patient care. Under certain circumstances, SIRS can progress onto its more severe and deleterious counterpart, sepsis. A quantitative marker for potential outcomes provides clinicians a standard to urgently guide their clinical decision making regarding a patient who may not initially appear critically ill but has the potential for becoming so. NT-proBNP has been studied as a predictor of mortality in critically ill patients with sepsis [7,8]. In contrast, our cohort consisted of children with SIRS and varying severity of illness. In children with sepsis, the cut-off value of NT-proBNP for heart failure was 1268 to 1525 pg/mL [13]. Another report described the cut-off value of NT-proBNP for mortality was 11,200 pg/mL in children with sepsis [8]. Our study showed the cut-off

values of NT-proBNP were 818 to 3034 pg/mL for morbidity and 29,988 pg/mL for mortality. We compared the area under the curve values in the ROC curve analysis of different biomarkers in our cohort. The SIRS scale was the best prognostic marker, followed by NT-proBNP and eGFR. These findings suggest that elevated NT-proBNP levels may be useful in predicting morbidity and mortality in SIRS.

#### 4.1. Study limitations

This was a retrospective study with inherent limitations. Our cohort had a small sample size. Our retrospective study design did not allow us to obtain the accurate timing of blood draw and fluid resuscitation. There was selection bias as patients appeared more likely to have a NT-proBNP level drawn if there were presumed to be severely ill. Future studies will need to be conducted in a prospective manner to eliminate the inherent limitations of a retrospective study and to confirm our

findings.

#### 5. Conclusion

Elevated NT-proBNP levels were associated with increased morbidity and possibly may be utilized as a useful predictor for morbidity and mortality in children with SIRS in the future.

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#### Declaration of Competing Interest

The authors declare that they have no conflict of interest.

#### Appendix A. List ICD-9 and ICD-10 codes to generate a list of patients

ICD code	Diagnosis
995.90	SIRS, NOS
995.91	SIRS due to infectious process
995.92	SIRS due to infectious process with acute organ dysfunction
995.93	SIRS due to non-infectious process with acute organ dysfunction
038.0	Streptococcal septicemia
038.10 to 038.19	Staphylococcal septicemia (with variants)
038.2	Pneumococcal septicemia
038.3	Sepsis due to anaerobes
038.40	Septicemia due to gram-negative organism, unspecified
038.41	Septicemia due to <i>Haemophilus influenzae</i>
038.42	Septicemia due to <i>Escherichia coli</i>
038.43	Septicemia due to pseudomonas
038.44	Septicemia due to Serratia
038.49	Other septicemia due to gram-negative organisms
038.8	Other specified septicemias
038.9	Unspecified septicemia
785.52	Septic shock
785.59	Other shock without mention of trauma
790.7	Bacteremia
A40.0 to A41.9	Sepsis due to organism
R65.20	Severe sepsis without septic shock
R65.21	Severe sepsis with septic shock
R65.10	SIRS of non-infectious origin without acute organ failure
R65.11	SIRS of non-infectious origin with acute organ failure
R78.81	Bacteremia

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