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NT-Pro-BNP and echocardiography for the early assessment of cardiovascular dysfunction in neonates with sepsis

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Abstract

To investigate the predictive manner of N-terminal fragment of brain natriuretic peptide (NT-Pro-BNP) and echocardiography in the early assessment of cardiovascular dysfunction (CVD) in neonates with sepsis, we recruited 108 neonates with sepsis in intensive care units and divided them into a sepsis with CVD (sepsis + CVD) group (n = 48) and a sepsis only group (n = 60). Neonates with other infections (n = 65) constituted the control group. Clinical, laboratory, and bedside echocardiography findings were evaluated. Compared to both the sepsis only and control groups, the sepsis + CVD group showed an earlier onset of symptoms [52.94 (0–185.6) h], higher NT-Pro-BNP levels (P = .02), a higher Tei index (0.52 + 0.03; P = .03), and lower ejection fraction (62.61% ± 12.31%, P < .05). Compared to the control group, the sepsis + CVD group exhibited hematogenous etiology (P < .05), lower albumin (ALB) levels (P = .04), lower white blood cell counts (P = .03), a higher high-sensitivity C-reactive protein/ALB ratio, and a larger right-ventricle-inner diameter (10.74 + 2.42 mm; P = .01). CVD in the septic neonates could be predicted by either NT-Pro-BNP levels (cut-off: 12,291.5 pg/L; sensitivity, 80%; specificity, 79%; area under the curve-receiver operating characteristic, 0.81) or Tei index (cut-off: 0.45; sensitivity, 74%; specificity, 77%; area under the curve-receiver operating characteristic, 0.78). NT-Pro-BNP levels and echocardiography can be used to determine early onset of CVD in neonatal sepsis, which facilitates timely pharmacological interventions and treatment.

Abbreviations: ALB = albumin, AUC = area under the curve, BNP = brain natriuretic peptide, BP = blood pressure, CRP = C-reactive protein, cTnI = troponin I, CVD = cardiovascular dysfunction, LV = left ventricle, LVEF = left ventricular ejection fraction, NICUs = neonatal intensive care units, NT-Pro-BNP = N-terminal fragment of brain natriuretic peptide, PASP = pulmonary artery systolic pressure, RV = right ventricle.

Keywords: albumin, brain natriuretic peptide, C-reactive protein, echocardiography, neonatal sepsis

1. Introduction

Sepsis refers to a systemic inflammatory response syndrome caused by local or systemic infections, affecting almost 3 million infants worldwide (22 per 1000 live births), with an estimated mortality rate of 11% to 19%.[1] Severe sepsis and septic shock are main causes of morbidity and mortality in critically ill patients.[2] The incidence of septic shock has been reported to reach 1.3% among patients in neonatal intensive care units (NICUs).[3] Cardiovascular dysfunction (CVD) manifested by reduced blood pressure (BP), metabolic acidosis, and lagging capillary refill has been reported to occur with severe sepsis at a prevalence as high as 70.2%.[4] A postmortem necropsy study revealed heavy myocardial injury in patients with sepsis and/or septic shock even in the absence of signs and symptoms.[5,6] Therefore, early prediction of CVD in neonatal sepsis patients is a critical clinical issue.

Sepsis develops after the intrusion of pathogens and endotoxins and is mediated by various endocrine inflammatory factors. A previous study showed that hypoalbuminemia and high levels of procalcitonin, interleukin-6, and white cell counts are indicative of poor outcomes in severely affected children,[7] but all of the markers showed a limited specificity and sensitivity for predicting CVD.

Cardiomyocytes with fluid overload secrete brain natriuretic peptide (BNP) to maintain fluid balance,[8] which dilates blood

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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vessels, promotes sodium excretion, and prevents vasoconstriction. BNP has been considered a specific indicator of ventricular dysfunction. Inflammatory and endothelial modulators in sepsis enhance BNP production, which also correlates with vasopressor support and renal injury.[9] High BNP levels are an independent risk factor of in-hospital mortality and hospital readmission for patients with CVD.[10–12] Plasma levels of N-terminal fragment of brain natriuretic peptide (NT-Pro-BNP) positively correlate with the severity of CVD in both adults and neonates.[13] Moreover, a high BNP level manifests itself in severe sepsis, stroke, neonatal patent ductus arteriosus, and persistent pulmonary hypertension, exhibiting similar fluctuation with C-reactive protein (CRP) and interleukin-1 levels.[14]

Doppler echocardiography serves as another typical approach to assess cardiac structure and function. Sepsis-related CVD presents a <50% decrease in cardiac output or left ventricular ejection fraction (LVEF),[15] and right cardiac dysfunction accounts for a considerable portion of septic CVD.

Despite the evidence described above, the biomarkers and echocardiography parameters relevant to neonatal septic CVD have yet to be fully elucidated. This study aimed to address this gap.

2. Materials and Methods

2.1. Patients

Neonates who were diagnosed with sepsis and admitted to the NICU of Liaocheng People's Hospital between January 2015 and December 2017 were included in this retrospective study. Patients with heart failure due to nonsepsis etiologies or showing myocarditis, cardiac malformation, genetic metabolic disease, or incomplete clinical data at admission were excluded from the study.

The diagnosis of sepsis was based on the recommendation of the International Pediatric Sepsis Forum in 2015.[16] Patients with one of the following features even after a 40 mL/kg/h isotonic intravenous fluid bolus administration were diagnosed with CVD[16]: a decrease in BP (hypotension, <5th percentile for age, systolic BP < 2 standard deviations below normal for age, taking a vasoactive drug to maintain BP), unexplained metabolic acidosis with a base deficit > 5.0 mEq/L, arterial lactate > 2 times the upper limit of the normal range, oliguria (urine output < 0.5 mL/kg/h), prolonged capillary refill (>5 seconds), >38°C of core-to-peripheral temperature gap, and compensated and decompensated shock.[17]

Finally, 108 patients with sepsis were included in this study. These patients were divided into 2 groups: normal cardiovascular (n = 48) and CVD (n = 60). Neonates with generalized infection in the same period were included in the control group (n = 65).

2.2. Biomarker measurements

The neonate's venous blood was collected when the patients were admitted to the hospital and immediately centrifuged to obtain the serum. NT-Pro-BNP levels were determined using a commercial kit (Model YZB/CAN 91001, Canada Response Biomedical, Burnaby, Canada) with a full-automatic enzyme immunochemical analyzer. Prealbumin, white blood cell count, platelet count, albumin (ALB), CRP, hs-CRP/ALB, creatine kinase MB, and troponin I (cTnI) serum levels were also measured.

2.3. Echocardiography

Experienced sonographers conducted bedside transthoracic echocardiography at the onset of sepsis using a Mylab Touch type portable Italian Yum Sheng Color Doppler Ultrasound with a 5 MHz probe to ensure both resolution and penetration of signals. All images were read 3 times to derive the average of each parameter. All neonates were laid on their backs or left sides in a resting state. The long axis of the left ventricle (LV) near the sternum and the standard apical 4-chamber axis views were taken. The left atrial diameter, LV end-diastolic dimension, left posterior wall thickness, end-diastolic interventricular septum, and right ventricular end-diastolic diameter were measured at the long axis of the LV near the sternum and standard apical 4-chamber cardiac sections. LVEF was determined using the Simpson's rule. The Tei index, defined as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time, was also calculated.[18] The estimation of pulmonary artery systolic pressure (PASP) in the absence of pulmonary stenosis was based on the Bernoulli equation (PASP = $4V^2$ + right atrial pressure, where V is the maximal systolic velocity of the regurgitant jet).[19]

2.4. Neonatal critical case score

First described in China in 2001,[20] the neonatal critical case score is an objective and effective neonatal disease-scoring index that includes 10 items. A total score of >90 is considered non-critical, 70 to 90 critical, and <70 extremely critical. Newborns who meet one or more of the individual indicators are also judged as critical.

2.5. Ethical statement

This study was approved by the Institutional Human Research Ethics Committee of Liaocheng People's Hospital. Written informed consent was obtained from the guardians of each participant. All patient/control data were retrospectively retrieved from electronic medical records.

2.6. Statistical analyses

The sample size of the case-control study was calculated using the exposure rate of study factors in the control group or population (P 0), the estimated value of the correlation intensity between research factors and disease (i.e., odds ratio [OR]), and the significance level of the statistical test hypothesis (i.e., type I error [false positive] probability [a, .05] and statistical test hypothesis [1-B] beta or the type II error [i.e., false negative]). The data were analyzed using SPSS software (Version 20, SPSS Inc., Chicago, IL). If the data were normally distributed, intergroup comparisons were conducted using analysis of variance followed by a post hoc test. Non-normally distributed data are presented as median (M) and quartile ranges (25th percentile–75th percentile). Intergroup comparisons were performed using either the Mann–Whitney rank sum test or the Chi-square test. A linear correlation was estimated between parameters. Logistic regression analysis was used to determine the risk factors of LV dysfunction. Receiver operating characteristic curves and area under the curve (AUC) were established to determine the sensitivity and specificity of the variables. P values < .05 were considered statistically significant.

3. Results

3.1. Demographics and clinical characteristics of patients

This case control study included 108 neonates (77 males and 31 females) who met the diagnostic criteria of sepsis and were admitted to the NICU between January 2015 and December 2017. Among these patients, 48 presented with CVD (sepsis + CVD group) and 60 did not (sepsis only group). A total of 65 cases (46 males and 19 females) with generalized infection in the

same period were enrolled in the control group. Table 1 shows the demographics and clinical characteristics of these patients. The mean gestational ages at delivery were 35.29 ± 3.00 and 36.38 ± 3.17 weeks, the mean birth weights were 2.65 ± 0.88 and 2.61 ± 0.90 kg, and the times of onset were 52.94 hours (0–185.6 hours) and 53.89 hours (0–170.55 hours) in the sepsis + CVD and sepsis only groups, respectively. The control group had a mean gestational age at delivery of 36.50 ± 2.22 weeks, mean birth weight of 3.05 ± 0.82 kg, and time of onset of 80 hours (18.8–202.29 hours).

Pulmonary infection was observed in 59 cases (54.6%), hematogenous infection in 40 cases (37.0%), and gastrointestinal infection in 9 cases (8.3%) in the sepsis and sepsis + CVD groups. In the control group, pulmonary infection, hematogenous infection, and abdominal infections were found in 40 (62.2%), 21 (31.1%), and 4 (6.67%) cases, respectively. The proportion of pulmonary infection cases in the sepsis + CVD group was significantly higher than that in the sepsis only ($P < .05$) and control groups ($P < .05$), and the proportion of hematogenous infection in the sepsis + CVD group was significantly higher than that in the control group ($P < .05$).

Five patients died in the sepsis + CVD groups, and no mortality was observed in the sepsis only or control groups. The proportion of critical cases in the septic patients reached 86.1%, which was significantly higher than the control group ($P = .01$).

3.2. Laboratory parameters

NT-Pro-BNP levels in the sepsis + CVD group [20,230.6 (15,890–35,000) pg/L] were significantly higher than those of the sepsis only and control groups (both $P < .05$). ALB levels and white blood cell counts in the control group were significantly higher, whereas the cTnI levels and hs-CRP/ALB ratio were significantly lower compared to the sepsis group ($P < .05$). However, differences in creatine kinase MB, CRP, and prealbumin levels were not statistically significant between the control and sepsis groups ($P > .05$).

3.3. Echocardiography indices

The inner right ventricle (RV) diameter in the sepsis + CVD group (10.74 ± 2.42 mm) was significantly higher than that in the control group ($P < .05$), but there was no statistically significant difference between the sepsis + CVD and sepsis only group ($P > .05$). The differences in the inner diameters of the other 3 chambers between the sepsis and control groups were not statistically significant. The Tei index was significantly higher in the sepsis + CVD group, reaching 0.52 ± 0.03 mm, compared to the other 2 groups. The LVEF was significantly lower in the sepsis + CVD group (62.61% ± 2.56%) compared to the control and sepsis only groups. The PASP level was higher in the sepsis + CVD group (52.25 ± 14.12 mm Hg) compared to the other 2 groups.

3.4. Risk factors of CVD

Univariate regression analysis was used to identify independent risk factors of CVD in sepsis (Table 2). NT-Pro-BNP levels, LVEF, Tei index, ALB levels, leukocyte counts, cTnI, and the hs-CRP/ALB ratio were significantly different between the sepsis + CVD and sepsis only groups. These parameters were

Table 1

Baseline and clinical characteristics of the enrolled subjects.

	Sepsis + CVD group	Sepsis only group	Control group	t/χ^2	*P*
Patient background					
Number of cases, n	48	60	65		
Gestational age (w, $X \pm S$)	35.29 ± 3.00	36.38 ± 3.17	36.50 ± 2.22	1.26	0.22
Body weight (kg, $X \pm S$)	2.65 ± 0.88*	2.61 ± 0.90	3.05 ± 0.82	2.02	0.05
Time of onset (h) (M (P25–P75))	52.94 (0–185.6)*†	53.89 (0–170.55)*	80 (18.8–202.29)	6.72	<0.01
Single critical case (n, %)	47 (97.9)*†	46 (76.7)	38 (58.5)	6.46	0.01
Mortality rate (n, %)	5 (4.6)	0 (0)	0 (0)	12.56	0.00
Infection sites (case, %)					
Pulmonary infection	24 (50.8)*†	35 (58.3)	40 (62.2)		
Hematogenous	20 (41.5)*	20 (34.8)	21 (31.1)		
Abdominal	4 (7.7)	5 (8.7)	4 (6.67)	6.46	0.01
Laboratory parameters					
ALB (g/L, $X \pm S$)	24.1 ± 3.8*	26.6 ± 3.2	27.8 ± 3.6	3.43	0.04
PA (g/L, $X \pm S$)	55.5 ± 26.6	59.4 ± 25.4	65.7 ± 22.2	0.56	0.14
WBC ($\times 10^9$/L)	12.7 (3.65–18.9)*	11.73 (8.89–17.7)	15.4 (9.93–23.2)	5.12	0.03
PLT ($\times 10^9$/L)	187 (112–239)	196 (124.0–287.2)	215 (134.0–216.0)	0.77	0.38
BNP (pg/L) (M (P25–P75))	20,230.6 (15,890–35,000)*†	13,057.6 (8946–35,000)*	7324.5 (2426.5–13,890)	5.75	0.02
CRP (mg/L) (M (P25–P75))	9.96 (3.5–32.3)*	3.67 (2.5–11.1)	3.89 (2.5–12.1)	0.79	0.38
hs-CRP/ALB (M (P25–P75))	0.33 (0.29–0.81)*	0.25 (0.20–0.76)*	0.06 (0.00–0.21)	6.1	0.01
CKMB (mmol/L, $X \pm S$)	144.28 ± 18.21	105.88 ± 14.06	79.90 ± 19.03	0.27	0.61
cTnI	3.37 ± 2.13*†	2.16 ± 0.03*	1.02 ± 0.07	3.36	0.04
Echocardiography index					
LV diameter (mm)	14.74 ± 2.68	15.02 ± 2.97	15.45 ± 3.39	0.05	0.82
LA diameter (mm)	10.69 ± 2.01	11.16 ± 2.03	11.91 ± 1.72	2.79	0.1
RV diameter (mm)	10.74 ± 2.42*	8.67 ± 2.07	8.55 ± 1.41	6.76	0.01
RA diameter (mm)	14.77 ± 3.01	15.02 ± 2.92	15.41 ± 2.67	0.96	0.33
LVEF (%)	62.61 ± 12.31*†	67.14 ± 8.55	70.03 ± 2.08	52.23	<0.01
Tei index	0.52 ± 0.03*†	0.39 ± 0.02*	0.30 ± 0.04	5.08	0.03
PASP (mm Hg)	52.25 ± 14.13*†	41.15 ± 21.73	41.07 ± 27.73	8.87	0.00

ALB = albumin, BNP = brain natriuretic peptide, CKMB = creatine kinase-MB, CRP = C-reactive protein, cTnI = troponin I, CVD = cardiovascular dysfunction, LA = left auricle, LV = left ventricle, LVEF = left ventricular ejection fraction, PA = prealbumin, PASP = pulmonary artery systolic pressure, PLT = platelet count, RA = right auricle, RV = right ventricle, WBC = white blood cell.

*Compared to the control group, $P < .05$.

†Compared to the sepsis only group, $P < .05$.

Table 2

Independent risk factors for CVD in sepsis.

Index	β ± SE	Wald	OR (95% CI)	*P* value
ALB	–0.22 ± 0.13	2.78	1.03 (1.01–1.09)	.09
WBC	0.03 ± 0.04	0.46	0.76 (0.59–0.82)	.49
BNP	0.01 ± 0.02	9.92	8.73 (1.54–5.67)	.00
EF	1.99 ± 2.11	0.07	0.98 (0.96–1.20)	.36
RV	0.77 ± 0.03	0.86	1.01 (0.99–1.02)	.11
hs-CRP/ALB	0.63 ± 0.31	4.17	1.87 (1.03–3.40)	.04
cTnI	0.54 ± 0.16	8.12	1.71 (1.25–2.03)	.04
Tei index	0.01 ± 0.00	7.81	1.97 (1.26–2.87)	.02

ALB = albumin, BNP = brain natriuretic peptide, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular dysfunction, cTnI = troponin I, EF = ejection fraction, OR = odds ratio, RV = right ventricle, WBC = white blood cell.

included in the multivariate regression model shown in Table 2. The analysis revealed that NT-Pro-BNP levels, Tei index, cTNI levels, and hs-CRP/ALB ratio are independent risk factors of CVD in neonatal sepsis ($P < .05$).

Receiver operating characteristic analysis showed that NT-Pro-BNP levels and the Tei index exhibited good predictive values for assessing CVD in neonatal sepsis. NT-Pro-BNP levels at a cut-off value of 12,291.5 pg/mL exhibited a sensitivity of 80%, specificity of 79%, and AUC of 0.81. The Tei index at a cut-off value of 0.45 showed a sensitivity and specificity of 74% and 77%, respectively, with an AUC of 0.78. At a cut-off value of 0.10, the hs-CRP/ALB ratio showed a sensitivity and specificity of 76% and 76.3%, respectively, with an AUC of 0.77 (Table 3).

4. Discussion

The incidence of septic shock in neonates admitted to the NICU is 1.3%, with gram-negative bacteria accounting for 38% of infections and 62.5% of deaths. CVD is a complicated organ failure resulting from the dynamic adaptation of the cardiovascular system in response to sepsis, host immune response, and resuscitation. Therefore, it is critical to evaluate heart function in children at an early stage during sepsis. NT-Pro-BNP levels can be used as a marker of early CVD, which when combined with bedside echocardiography, may be used in the early diagnosis of CVD in children with sepsis.

In our study, there were 5 deaths in the sepsis group and no deaths in the control group, which is consistent with the report that the abnormal LV or RV contractions and dilation are associated with poor prognosis in severe sepsis patients.[21] However, patients with LV or RV insufficiency who survived for more than 5 days showed an improved LVEF, e/e' (Doppler tissue imaging velocities) ratio, and tricuspid annular plane systolic excursion, suggesting a reversibility of sepsis-associated CVD.[22]

A previous meta-analysis indicated that elevated BNP or NT-Pro-BNP levels served as a powerful predictor of sepsis-related fatality.[23] In the present study, the proportion of critical cases in the sepsis + CVD group reached 97.9%, which was significantly higher than that of the other 2 groups.

Table 3

ROC analysis on the predictive ability of risk factors for CVD.

Parameter	Sensitivity (%)	Specificity (%)	Cut-off value	AUC area
BNP	80	79	12,291.5	0.81
Tei index	74	77	0.45	0.78
hs-CRP/ALB	76	76.3	0.10	0.77

ALB = albumin, AUC = area under the curve, BNP = brain natriuretic peptide, CRP = C-reactive protein, CVD = cardiovascular dysfunction, ROC = receiver operating characteristic.

We found that the sepsis groups had significantly higher NT-Pro-BNP levels and a CRP/ALB ratio compared to the control group. In the sepsis + CVD group, NT-Pro-BNP levels increased substantially relative to the sepsis only group, suggesting an association of NT-Pro-BNP with the severity of sepsis. A previous study[24] found that NT-Pro-BNP levels changed with the sequential organ failure assessment score, further supporting our findings. In our multivariate analysis, NT-Pro-BNP acted as a predictive marker for CVD in sepsis, with the sensitivity and specificity of 80% and 79%, respectively, when 12,291.5 pg/mL was set as the cut-off point, consistent with the previous studies.

Serum ALB levels decrease in the acute-phase of infections, and lower ALB levels are observed in 40% to 50% of critically ill patients.[25] Serum ALB restores the lipopolysaccharide-impaired flow-dependent endothelial dilation in the mesenteric arteries via activating endothelial nitric oxide synthase.[26] In this study, the multivariate analysis revealed that the association between hypoalbuminemia and adverse outcomes, such as death, was independent of other factors. This finding is consistent with the results of a previous study involving 108 patients, in which hypoalbuminemia appeared much more frequently in the sepsis + CVD group than in the control group.

In the present study, leukocyte counts were not significantly different between the sepsis + CVD and sepsis only groups in the logistic regression analysis model. It is important to note that leukocyte and differential counts are common indicators of neonatal infection. However, their wide reference range and susceptibility to various factors prevent them from being reliable markers to assess infection.

It has been reported that the specificity of CRP alone for monitoring neonatal bacterial infections is insufficient.[27] However, the hs-CRP/ALB ratio has been considered a sensitive predictor of mortality and prognosis for children with severe infections (with an AUC of 0.77).[28] In the present study, CRP levels were not significantly different between the 3 groups,[18] which may be due to the undeveloped immune system of the neonates, for which CRP does not increase during bacterial infections despite being an acute-phase protein secreted by the liver.[29]

Echocardiography analyses in the present study demonstrated an increased RV inner diameter in the CVD group. The Tei index is used to assess systolic and diastolic function in the heart, which is stable and unaffected by heart rate and cardiac preload. The Tei index in this study was significantly higher in the sepsis + CVD group compared to the sepsis only and control groups.

The LVEF was lower in the sepsis + CVD group than in the sepsis only and control groups. Right heart dysfunction accounts for a large proportion of sepsis-related cardiac impairment, so it is clinically illogical to use the LVEF alone to determine sepsis-induced heart dysfunction. We repeated the echocardiography examination after the patient's condition was improved and found that all of the abnormal parameters recovered to some extent. The logistic regression model showed that NT-Pro-BNP levels, the Tei index, and the hs-CRP/ALB ratio were independent risk factors for CVD in neonates with septic shock.

There are several limitations in our study. First, the single-center retrospective observational study design might introduce bias. For example, we were unable to use matched controls. Infection onset time and birth weight were significantly different between the sepsis and control groups. The single-center clinical and laboratory expertise could also influence the overall results. We did not conduct statistical power analysis to determine the optimal number of patients/controls included in our study. Finally, we did not consider all of the other factors that might have contributed to sepsis, such as the need for mechanical ventilation or duration of hospitalization. Further investigation is warranted to elucidate the mechanism underlying the correlation between plasma NT-Pro-BNP levels and inflammatory factors. A prospective cohort study should be designed to clarify

the predictability of NT-Pro-BNP levels and echocardiography on early onset of CVD in neonatal sepsis.

In conclusion, NT-Pro-BNP levels and bedside echocardiography can predict CVD early in septic neonates, which may facilitate the timely use of vasoactive drugs in the clinic to prevent CVD.

Author contributions

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