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Female-Specific Association of Plasma N-Terminal Pro-Brain Natriuretic Peptide With Organ Dysfunction and Prognosis in Sepsis: A Retrospective Study

OBJECTIVES: The plasma level of N-terminal pro-brain natriuretic peptide is regulated by sex hormones. It has been controversial whether N-terminal pro-brain natriuretic peptide is a prognosis marker for sepsis. The aim of this study is to examine the sex-dependent association of plasma N-terminal pro-brain natriuretic peptide with organ dysfunction and mortality of sepsis patients.

DESIGN: In this retrospective study, the association between plasma N-terminal pro-brain natriuretic peptide concentration on the day of sepsis diagnosis and the degree of organ dysfunction, occurrence of septic shock, or 30-day mortality in both male and female patients was analyzed.

SETTING: This study was conducted in the Sepsis Laboratory at the Huaihe Hospital of Henan University in China.

PATIENTS: Diagnoses of sepsis, and septic shock, were based on the recently revised criteria (Sepsis 3.0). All sepsis patients (517) hospitalized in the respiratory ICU of the Huaihe Hospital from June 2016 to December 2019 were enrolled in this study.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: No significant difference was found in the age, occurrence rate of septic shock, 30-day mortality, or degree of organ dysfunction between male and female patients. Median concentration of plasma N-terminal pro-brain Natriuretic peptide was higher by 93.48% in female than male patients. A significant association was found between N-terminal pro-brain natriuretic peptide and septic shock or 30-day mortality in female, but not in male patients of community- or hospital-acquired sepsis. N-terminal pro-brain natriuretic peptide levels correlated to functional deficiencies of the cardiac and nervous systems, only in female patients.

CONCLUSIONS: The plasma N-terminal pro-brain natriuretic peptide level is a female-specific prognosis indicator of septic shock and mortality.

KEY WORDS: female-specific; mortality; N-terminal pro-brain natriuretic peptide; organ dysfunction; prognostic marker; sepsis; septic shock

Sepsis is life-threatening organ dysfunction caused by an infection and is associated with 11 million deaths annually worldwide (1, 2). Due to the unavailability of effective drugs, the treatment of sepsis patients largely relies on functional support of critical organ systems. Accurate and timely

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evaluation of the patient's condition may provide guidance to treatment strategies.

N-terminal pro-brain natriuretic peptide (NT-proBNP) and its counterpart brain natriuretic peptide (BNP) are cleavage products of proBNP that is secreted primarily by ventricular myocardial cells (3, 4). The secretion of BNP is regulated by sex hormones. In particular, female hormone estradiol augments the plasma concentration of BNP, whereas the male hormone, testosterone, has an opposite effect (5, 6). BNP levels in healthy populations are about two-fold higher in women than men (7). Such differences are largely diminished in patients of advanced age at the primary care facility, probably due to reduced levels of sex hormones (8). Compared with healthy controls, sepsis patients have been shown to have higher plasma levels of estradiol and lower testosterone than healthy controls (9, 10). Among sepsis patients, males have lower estradiol and slightly higher testosterone than females (9). It is not known whether there is a sex-associated difference in BNP levels in sepsis patients.

Plasma levels of both BNP and NT-proBNP are well-accepted diagnostic and prognostic markers for congestive heart failure. Since the first report of elevated plasma BNP in septic shock patients by Witthart et al (11), many studies have shown that plasma BNP or NT-proBNP is positively associated with illness severity in sepsis patients with or without cardiac dysfunction (12–18). However, such a conclusion has been challenged by contradictory findings showing no, or only weak, association between BNP and sepsis mortality (18–22). On the other hand, BNP appears to have a stronger association with the mortality of female hospitalized patients or female acute dyspnea patients in particular (23, 24). Perhaps more pertinently, it was recently reported that plasma BNP concentration, at the onset of sepsis, negatively correlates to postsepsis physical recovery only in female patients (25). It is not known whether plasma BNP is associated with sepsis prognosis, in a sex-dependent manner.

MATERIALS AND METHODS

Ethical Statement

This retrospective study and the waiver of informed consent were approved by the Medical Ethical Committee of the Henan University (Protocol number: 2016117).

Patients

All patients hospitalized in the respiratory ICU in the Huaihe Hospital of Henan University from June 2016 to December 2019 were screened according to the recently revised diagnostic criteria of sepsis (i.e., Sequential [Sepsis-related] Organ Failure Assessment [SOFA] score ≥ 2 [1]). Septic shock refers to sepsis in patients who required vasopressors to maintain a mean arterial pressure greater than or equal to 65 mm Hg and a plasma concentration of lactate greater than 2 mM on the same day during hospitalization (1). The 30-day mortality was determined from hospital records or follow-up. Community-acquired sepsis (CAS) refers to patients diagnosed within 48 hours after admittance, whereas patients of hospital-acquired sepsis (HAS) were diagnosed after the admittance for 48 hours. The site of infection was categorized by anatomical systems. Charlson comorbidity index was used to categorize comorbidities (26).

NT-proBNP and Other Clinical Tests

Blood was collected in a standard EDTA-containing tube and centrifuged at 2,000g for 10 min. The resultant plasma was subjected to NT-proBNP analysis using a commercial kit with a sensitivity range between 18.0 and 35,000.0 pg/mL (NT-proBNP; Wondfo Biotech, Guangzhou, China). The time interval from blood collection to BNP analysis was less than an hour. SOFA scores (1) and values of other blood tests performed on the same day were obtained from patients' records.

Statistical Analysis

Variables were expressed in median and interquartile ranges, unless otherwise specified. The Shapiro-Wilk test was used for the determination of Gaussian distribution of values, Spearman rank-order analysis for correlation (r_s), Mann-Whitney U test for comparisons of two groups, Kruskal-Wallis analysis of variance test followed by the Dunn's test for comparisons of multiple groups, receiver operating characteristic (ROC) curves for predictability of plasma NT-proBNP in the occurrence of septic shock or 30-day mortality, Fisher Z methods for the difference of correlation coefficients between male and female patients, Log-rank for comparison of Kaplan-Meier survival curves, and multiple Cox regression analysis for the effect of NT-proBNP

on the mortality, using the age, site of infection, and comorbidity as covariates. A two-sided p value of less than 0.05 was considered significant.

RESULTS

Patient Characteristics

A total of 517 patients diagnosed sepsis or septic shock, within which 315 were tested for plasma NT-proBNP on the day of diagnosis. As shown in **S-table 1** (<http://links.lww.com/CCX/A581>), no significant difference in the sex, age, occurrence rate of septic shock, 30-day mortality rate, or overall degree of organ dysfunction (SOFA_sum) was found between patients who were and were not tested for NT-proBNP, except that lung dysfunction was slightly more severe in the former group (SOFA_lung, 2.78 vs 2.53; $p = 0.004$).

The 315 patients who were tested for plasma NT-proBNP consisted of 214 males and 101 females (**Table 1**), including 142 CAS patients (45.08%) and 173 HAS patients (54.92%). The median time from ICU admission and sepsis onset of HAS patients was 7 days (4–15 d). No significant difference in the degree of organ dysfunction between CAS and HAS patients of male (7.83 ± 4.08 vs 7.29 ± 3.94 ; $p = 0.33$) or female (7.22 ± 4.13 vs 6.58 ± 3.96 ; $p = 0.48$). In addition, no significant difference was found in the age, duration of ICU stay, occurrence rate and duration of mechanical ventilation, composition of CAS and HAS patients, ratio of patients developing septic shock, or 30-day mortality rate between male and female patients (Table 1). Furthermore, the degree of overall organ dysfunction or dysfunction of most critical organ systems was not significantly different between males and

TABLE 1.
Demographics, Sequential Organ Failure Assessment Scores, and Prognosis of Sepsis Patients Included in the Study

Characteristics	Male		Female		p
Sex, n (%)	214 (67.94)		101 (32.06)		–
Age (yr), median (interquartile range)	71 (60–78)		73 (61.5–82)		0.17
Duration of respiratory ICU stay (d), median (interquartile range)	7.95 (3.59–14.08)		6.68 (3.93–13.08)		0.74
Intubated, n (%)	109 (50.93)		44 (43.56)		0.24
Intubation time (d), median (interquartile range)	5.24 (2.23–8.91)		4.05 (1.91–6.07)		0.11
Community vs hospital acquired, n (%)	96/118 (44.86/55.14)		46/55 (45.54/54.46)		0.91
Septic shock, % (n , yes/total)	31.19 (63/202)		26.04 (25/96)		0.35
30 d mortality rate, % (n , dead/total)	43.32 (81/187)		46.51 (40/86)		0.62
Organ Dysfunction	Mean (95% CI)	n	Mean (95% CI)	n	p
SOFA_sum	7.55 (7.01–8.09)	214	6.84 (6.05–7.63)	101	0.1
SOFA_lung	2.81 (2.69–2.93)	200	2.73 (2.54–2.92)	96	0.66
SOFA_heart	1.16 (0.92–1.40)	214	1.06 (0.72–1.40)	101	0.64
SOFA_liver	0.45 (0.34–0.55)	201	0.26 (0.13–0.39)	97	0.03
SOFA_kidney	0.82 (0.66–0.99)	210	0.63 (0.44–0.82)	101	0.36

SOFA = Sequential Organ Failure Assessment, SOFA_organ = SOFA score of individual organ system, SOFA_sum = total SOFA score. Dash indicates that no comparison between male and female groups was performed. Boldface values are parameters that are significant different between male and female patients ($p < 0.05$).

females (Table 1). Interestingly, male patients appeared to have suffered more severe liver dysfunction than females ($p = 0.03$), even though liver deficiency was the mildest among all six organ systems.

Correlation of NT-proBNP Concentration With Organ Dysfunction

The median concentration of plasma NT-proBNP was 2.83 $\mu\text{g/L}$ (Table 2) in all patients, which is consistent with previous reports (14, 18). There was no significant difference in NT-proBNP concentrations between CAS (2.56 $\mu\text{g/L}$ [0.70–8.45 $\mu\text{g/L}$]) and HAS patients (2.97 $\mu\text{g/L}$ [0.80–9.84 $\mu\text{g/L}$]; $p = 0.50$). However, the intubated patients (4.02 $\mu\text{g/L}$ [0.94–13.8 $\mu\text{g/L}$]) had a higher level of NT-proBNP than nonintubated patients (2.08 $\mu\text{g/L}$ [0.67–7.92 $\mu\text{g/L}$]; $p = 0.036$).

As shown in Table 2, patients resulted from an infection of the urinary system, among all sites of infection, had the highest NT-proBNP concentration (9.82 $\mu\text{g/L}$). Furthermore, the dysfunction of kidney, among all organ systems included in the organ failure assessment for sepsis diagnosis (1), was associated with the highest NT-proBNP concentration (8.50 $\mu\text{g/L}$). Consistently, NT-proBNP exhibited the highest level of correlation with renal dysfunction ($r_s = 0.49$) (S-table 2, <http://links.lww.com/CCX/A582>), followed by abnormal coagulation ($r_s = 0.26$) and cardiac function ($r_s = 0.13$). No significant correlation was found between NT-proBNP and dysfunction of the liver, lung, or nervous system. Consistently, NT-proBNP had the highest correlation level with plasma creatinine ($r_s = 0.49$) and blood urea nitrogen ($r_s = 0.42$), followed by coagulation variables such as international normalized ratio ($r_s = 0.30$) and prothrombin time activity ($r_s = -0.30$).

Female-Specific Association of NT-proBNP With Septic Shock and 30-Day Mortality

The plasma concentration of NT-proBNP in female (4.45 $\mu\text{g/L}$ [1.19–16.13 $\mu\text{g/L}$]) was 93.48% higher than male patients (2.30 $\mu\text{g/L}$ [0.67–7.70 $\mu\text{g/L}$]; $p = 0.012$) (Fig. 1A). The difference in NT-proBNP between female and male was also evident in CAS group (3.36 vs 1.97 $\mu\text{g/L}$; $p = 0.10$) and HAS group (6.12 vs 2.83 $\mu\text{g/L}$; $p = 0.04$). Significant difference in NT-proBNP concentrations was found between those with and without septic shock in female patients (no shock vs shock: 2.42 [0.99–12.20] vs 12.53 $\mu\text{g/L}$ [4.22–30.51 $\mu\text{g/L}$]; $p = 0.014$) (Fig. 1B), but not in all patients (2.08 vs 4.64

$\mu\text{g/L}$; $p = 0.10$) or male patients (1.96 [0.62–7.67] vs 3.36 $\mu\text{g/L}$ [0.72–7.33 $\mu\text{g/L}$]; $p = 0.53$). Similarly, the difference in NT-proBNP concentrations was significant between nonintubated (2.89 $\mu\text{g/L}$ [0.69–8.72 $\mu\text{g/L}$]) and intubated female patients (7.00 $\mu\text{g/L}$ [1.62–27.18 $\mu\text{g/L}$]; $p = 0.041$), but not in male patients (nonintubated vs intubated: 1.85 [0.63–6.79] vs 3.36 $\mu\text{g/L}$ [0.71–8.21 $\mu\text{g/L}$]; $p = 0.14$).

Importantly, individuals who died within 30 days after sepsis diagnosis had a higher NT-proBNP level (5.41 $\mu\text{g/L}$ [1.15–14.34 $\mu\text{g/L}$]) than survivors (1.65 $\mu\text{g/L}$ [0.61–8.53 $\mu\text{g/L}$]; $p = 0.001$) (Fig. 1C). The NT-proBNP concentration was higher by 459% in female nonsurvivors (7.95 $\mu\text{g/L}$ [4.33–29.40 $\mu\text{g/L}$]) than survivors (1.43 $\mu\text{g/L}$ [0.56–7.35 $\mu\text{g/L}$]; $p < 0.0001$), but not significantly different between male survivors (1.96 $\mu\text{g/L}$ [0.66–8.97 $\mu\text{g/L}$]) and nonsurvivors (3.52 $\mu\text{g/L}$ [0.80–8.84 $\mu\text{g/L}$]; $p = 0.213$) (Fig. 1C). Similarly, NT-proBNP concentrations were significantly higher in female nonsurvivors than survivors in both CAS group (8.01 [1.70–26.26], $n = 20$, vs 1.43 $\mu\text{g/L}$ [0.56–7.35 $\mu\text{g/L}$], $n = 21$; $p = 0.011$) and HAS group (7.67 [4.71–26.05], $n = 25$ vs 1.53 $\mu\text{g/L}$ [0.49–7.79 $\mu\text{g/L}$], $n = 20$; $p = 0.003$). In contrast, no significant difference between male nonsurvivors and survivors in both the CAS patients (3.09 vs 1.97 $\mu\text{g/L}$; $p = 0.655$) and HAS patients (4.37 vs 1.76 $\mu\text{g/L}$; $p = 0.129$).

ROC analysis of the predictability of NT-proBNP for the 30-day mortality (Fig. 1D) showed area under the curve values of 0.62 (all patients), 0.55 (male), and 0.77 (female). The optimal cut off points of NT-proBNP were 2.91, 4.66, and 4.37 $\mu\text{g/L}$, with corresponding sensitivities of 63%, 45%, and 76% and specificities of 63%, 70%, and 75% for all, male, and female patients, respectively.

Comparison of 30-day survival curves of male and female patients did not reveal a significant difference ($p = 0.78$) (Fig. 2A). However, multiple Cox regression analysis (Fig. 2B), using the age, site of infection, and comorbidity as covariates, showed that each fold of increase in NT-proBNP concentration was accompanied by an elevation in hazard ratio of 8.8% in all patients ($p = 0.050$) and 31.9% in female patients ($p = 0.001$). No association between NT-proBNP concentration and the hazard ratio was found in male patients ($p = 0.988$).

The Association of NT-proBNP and Organ Dysfunction in Patients of Different Sexes

Consistent with being excreted primarily through urinary system (18), NT-proBNP displayed the strongest

TABLE 2.**Plasma N-Terminal Pro-Brain Natriuretic Peptide Concentration in Sepsis Patients of Different Infection Sites, Comorbidities, and Dysfunctioning Organ Systems**

Category	n (%)	Age (yr), Median (IQR)	N-Terminal Pro-Brain Natriuretic Peptide (µg/L), Median (IQR)
Site of infection			
All	315 (100)	71 (61–80)	2.83 (0.72–8.89)
Respiratory	225 (71.43)	71 (61.5–80)	2.83 (0.73–8.21)
Digestive	41 (13.02)	71 (60–80)	4.59 (0.80–25.74)
Urinary	14 (4.44)	81 (62.75–90.75)	9.82 (3.31–30.73)
Neurologic	12 (3.81)	66.50 (52.25–75)	1.41 (0.70–1.97)
Others	18 (5.71)	–	–
Undefined	55 (17.46)	71 (61–78)	2.33 (0.58–14.30)
Charlson comorbidity index			
Cerebrovascular disease	44 (13.97)	73 (61–78)	3.23 (1.09–12.17)
Chronic lung disease	42 (13.33)	73.5 (65–82.5)	1.85 (0.57–5.81)
Congestive heart failure	15 (4.76)	80 (69–88)	6.58 (2.16–16.99)
Peripheral vascular disease	13 (4.13)	65 (54.5–74.5)	1.34 (0.86–8.33)
Cancer	12 (3.81)	72.5 (61.25–76)	7.38 (1.41–30.68)
Peptic ulcer disease	12 (3.81)	79 (69.25–85)	7.46 (4.45–26.09)
Renal disease	9 (2.86)	–	–
Diabetes	8 (2.54)	–	–
Liver disease	7 (2.22)	–	–
Paralysis	5 (1.59)	–	–
Neurologic disease	4 (1.27)	–	–
Rheumatologic disease/AIDS	0	–	–
Organ dysfunction ^a			
Lung	290 (92.06)	71 (60.75–79)	2.78 (0.72–8.97)
Heart	95 (30.16)	71 (59–80)	4.70 (0.91–14.35)
Liver	75 (23.81)	73 (55–79)	4.47 (0.70–12.06)
Kidney	124 (39.37)	69 (56–78)	8.50 (2.80–27.69) ^b
Coagulation	151 (47.94)	71 (59–81)	5.16 (1.34–12.53)
CNS	146 (46.35)	73 (59.75–82)	3.99 (0.73–10.37)

IQR = interquartile range.

^aPatients were included and grouped when the Sequential Organ Failure Assessment score of an organ system was ≥ 1 . The N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration of each organ dysfunction group was compared with the All patients group and other organ systems.

^bNT-proBNP concentration was significantly higher than the All patient ($p < 0.0001$), Lung ($p < 0.0001$), Liver ($p = 0.022$), and CNS ($p = 0.001$) groups. No significant difference in the concentration of plasma NT-proBNP was found between other organ dysfunction groups. Values of age and NT-proBNP are presented in median and interquartile ranges. The analysis was performed using the Kruskal-Wallis analysis of variance test, followed by Dunn's test under the two-tailed setting.

Dashes indicates that no comparison between male and female groups was performed.

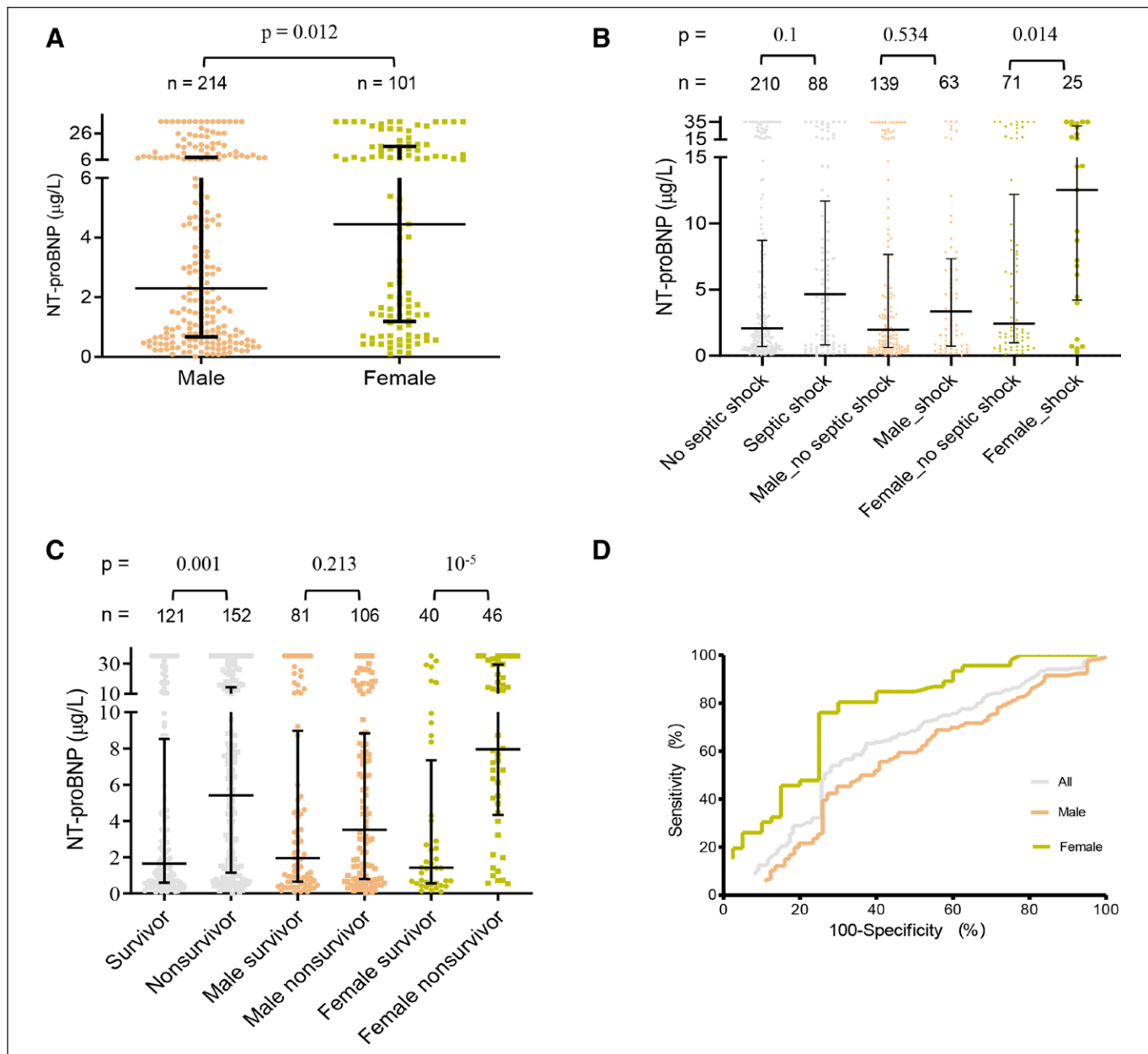


Figure 1. Female-specific association of plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) with septic shock and mortality. **A**, Comparison of plasma concentrations of NT-proBNP in male ($n = 214$) and female (101) sepsis patients. **B**, Comparisons of plasma concentrations of NT-proBNP in sepsis patients who did and did not develop septic shock. **C**, Comparisons of plasma concentrations of NT-proBNP in 30 d survivors and nonsurvivors. **A–C**, Mann-Whitney U test was used for group comparisons. Values are shown as median and interquartile ranges. **D**, Receiver operating curves were plotted to determine the area under the curve for the predictability of plasma NT-proBNP in 30 d mortality in all, male and female sepsis patients.

correlation with the kidney dysfunction score in both sexes (Table 3). Among the panel of organ dysfunction assessments and clinical tests, NT-proBNP showed significantly higher levels of correlation with the overall degree of organ dysfunction (SOFA_sum, 0.50 vs 0.20; $p = 0.005$), SOFA_heart (0.40 vs 0.02; $p = 0.001$) and SOFA_CNS (0.23 vs -0.05; $p = 0.02$) in females than males.

DISCUSSION

The results of this retrospective study clearly show a sex-dependent profile of plasma NT-proBNP in sepsis patients. Specifically, NT-proBNP concentration is approximately one-fold higher in female than in male patients. In addition, NT-proBNP level significantly correlates to the occurrence of septic shock and the

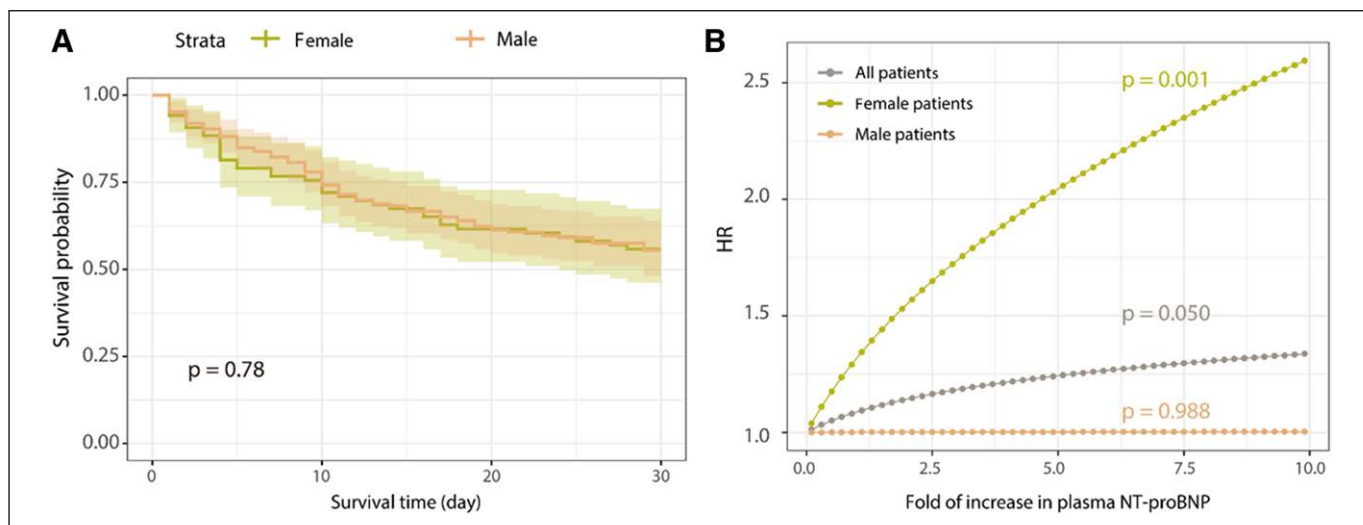


Figure 2. The association of plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) with the 30 d mortality of sepsis patients. **A**, The Kaplan-Meier survival curves of male and female sepsis patients were compared using the Log-rank method. **B**, Multiple Cox regression analysis was performed to determine the hazard ratio of every fold increase in plasma NT-proBNP in all, male and female sepsis patients. The concentration of NT-proBNP was converted by a logarithmic transformation based on 1.1–10.9. Age, site of infection, and comorbidity were used as covariates.

risk of mortality only in females. Furthermore, there is a stronger association between plasma NT-proBNP with dysfunctions of the cardiac and nervous systems in female than male patients.

The median age of patients in this study was 71 years with an interquartile range of 60–82 years. According to a previous report, plasma BNP concentrations of primary care patients of this age group are similar between males and females (8). In contrast to primary care patients, sepsis patients have elevated estradiol (9). In addition, male sepsis patients have a lower level of estradiol and a higher level of testosterone than their female counterparts (9). Given that estradiol is known to up-regulate plasma BNP, whereas testosterone has an opposite effect (5, 6), the difference in plasma NT-proBNP concentration may be attributable to distinct levels of sex hormones in female and male sepsis patients.

A number of studies have characterized the association of plasma BNP and/or NT-proBNP with the mortality of sepsis patients since Witthaut et al (11) first reported the increase of plasma BNP in septic shock patients (12–22). However, a consensus has not been reached due to contradicting results (18). The discrepancy may be due to limited sample size (< 100 subjects in most studies), heterogeneity of sepsis, the timing of BNP measurement, and the types of assays used (11–22). In this study of 315 patients, we found that

a significant association of plasma NT-proBNP with septic shock or 30-day mortality was present only in female patients. Therefore, plasma NT-proBNP could be a useful predictor of sepsis mortality for female patients but has little value for male patients.

Plasma BNP and NT-proBNP have been shown to be an independent predictor of outcome in hospitalized patients with or without heart failure (24, 27), suggesting the potential of plasma BNP as a mortality marker in various diseases. The female-specific association of BNP with mortality has been reported in patients with acute dyspnea (23). Interestingly, BNP level was found to be associated with postsepsis physical recovery only in females (26). These studies, together with our findings, suggest that plasma BNP is potentially a useful mortality predictor for female patients of a broader panel of diseases.

In addition to the well-characterized association of plasma NT-proBNP with dysfunctions of heart (the source organ of BNP) and kidney (the primary organ for NT-proBNP clearance), our correlation analysis revealed a significant association between plasma NT-proBNP and coagulation anomaly in both sexes, which appears to be stronger in females ($r_s = 0.40$) than males ($r_s = 0.23$). Furthermore, we found that NT-proBNP correlates to the degree of dysfunction of the cardiac as well as nervous system only in female patients. These phenomena may be attributable to the

TABLE 3.
Correlation Between N-Terminal Pro-Brain Natriuretic Peptide and Clinical Variables in Male and Female Sepsis Patients

Category	Male			Female			P
	r_s	p	n	r_s	p	n	
SOFA_sum	0.20	0.003	214	0.50	10 ⁻⁸	101	0.0046
SOFA_kidney	0.48	10 ⁻¹⁴	210	0.52	10 ⁻⁸	101	0.6632
SOFA_coagulation	0.23	0.0009	211	0.40	10 ⁻⁵	101	0.1217
SOFA_liver	0.10	0.17	201	0.07	0.49	97	0.8092
SOFA_heart	0.02	0.74	214	0.40	10 ⁻⁵	101	0.0010
SOFA_CNS	-0.05	0.48	213	0.23	0.02	101	0.0201
SOFA_lung	0.002	0.98	200	0.19	0.07	96	0.1260
Creatinine	0.47	10 ⁻¹²	206	0.59	10 ⁻¹⁰	99	0.1760
Blood urea nitrogen	0.41	10 ⁻⁹	205	0.48	10 ⁻⁷	100	0.4794
International normalized ratio	0.33	10 ⁻⁶	183	0.32	0.002	91	0.9315
Procalcitonin	0.32	10 ⁻⁵	172	0.22	0.04	85	0.4223
Prothrombin time	0.32	10 ⁻⁵	183	0.32	0.002	91	1.0000
Activated partial thromboplastin time	0.29	10 ⁻⁵	182	0.17	0.100	91	0.3297
α -hydroxybutyric dehydrogenase	0.25	0.004	132	0.35	0.004	67	0.4717
RBC distribution width coefficient of variation	0.24	0.0003	212	0.34	0.0006	101	0.3719
Lactate dehydrogenase	0.23	0.007	134	0.41	0.0006	66	0.1889
Fibrinogen degradation product	0.23	0.003	177	0.30	0.004	90	0.5662
Aspartate transaminase	0.21	0.002	208	0.22	0.03	99	0.9324
Mean platelet volume	0.21	0.002	201	0.30	0.003	94	0.4468
Creatine kinase isoenzymes M and B	0.20	0.02	134	0.03	0.79	66	0.2599
Platelet large cell ratio	0.20	0.004	201	0.30	0.003	93	0.4009
D-dimer	0.20	0.007	178	0.31	0.003	89	0.3710
Platelet distribution width	0.16	0.03	201	0.30	0.003	94	0.2421
Creatine kinase	0.04	0.68	134	0.27	0.03	66	0.1224
Lymphocyte, %	-0.21	0.002	212	-0.22	0.03	100	0.9320
Hemoglobin	-0.29	10 ⁻⁵	212	-0.26	0.009	101	0.7909
Fibrinogen	-0.22	0.003	183	-0.19	0.08	91	0.8097
RBCs	-0.25	0.0002	212	-0.17	0.09	101	0.4939
Platelets	-0.26	10 ⁻⁵	211	-0.26	0.008	101	1.0000
Plateletcrit	-0.28	10 ⁻⁵	201	-0.34	0.001	94	0.6000
Hematocrit	-0.28	10 ⁻⁵	212	-0.26	0.008	101	0.8601
Prothrombin time activity	-0.33	10 ⁻⁶	183	-0.33	0.001	91	1.0000
Albumin	-0.08	0.24	201	-0.27	0.008	98	0.1150

SOFA = Sequential Organ Failure Assessment, SOFA_organ = SOFA score of individual organ system, SOFA_sum = total SOFA score. Spearman rank-order correlation analysis was performed to determine the strength of associations between plasma N-terminal pro-brain natriuretic peptide concentration and values of SOFA and a variety of laboratory tests. The Fisher Z methods were used to compare the correlation coefficients of male and female groups. Boldface values are parameters that are significant different between male and female patients ($p < 0.05$).

female-specific association between BNP and mortality in patients with sepsis.

This retrospective study has a number of limitations and should be considered in future studies. For instance, NT-proBNP concentration and sepsis severity (assessed using SOFA, not Acute Physiology and Chronic Health Evaluation II scores) were restricted to the day of diagnosis, and the appropriateness of treatments was not assessed. Furthermore, all subjects enrolled in this study were from the respiratory ICU and may not possess a full spectrum of pathologic characteristics of sepsis patients in general. Even though the sample size (315 subjects) is larger than most previous studies (11–22), it is still rather limited. Finally, it is important to determine whether the female-specific association of NT-proBNP with sepsis prognosis also applies to younger populations.

CONCLUSIONS

Our data support a female-specific association between plasma NT-proBNP and sepsis prognosis. NT-proBNP has the potential to serve as perhaps the first female-specific indicator of sepsis mortality.

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