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...
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 females.

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

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 \((9.82 \mu g/L)\). 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 \((9.82 \mu g/L; p = 0.03)\), even though liver deficiency was not significantly different \((p = 0.03)\) even though liver deficiency was not significantly different \((p = 0.04)\) between male and female patients. No significant difference in NT-proBNP concentrations between those with and without septic shock in female patients \((2.97 \mu g/L [0.80–9.84 \mu g/L]; p = 0.036)\) and cardiac function \((r = 0.49)\) (S-table 2, http://links.lww.com/CCX/A582), followed by abnormal coagulation \((r = 0.26)\) and cardiac function \((r = 0.13)\). No significant correlation was found between NT-proBNP and dysfunction of the liver, lung, or nervous system. Consistently, NT-proBNP had the highest level of correlation with renal dysfunction \((r = 0.49)\) and blood urea nitrogen \((r = 0.42)\), followed by coagulation variables such as international normalized ratio \((r = 0.30)\) and prothrombin time activity \((r = -0.30)\).

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

The plasma concentration of NT-proBNP in female \((4.45 \mu g/L [1.19–16.13 \mu g/L])\) was 93.48% higher than male patients \((2.30 \mu g/L [0.67–7.70 \mu g/L]; p = 0.012)\) (Fig. 1A). The difference in NT-proBNP between female and male was also evident in CAS group \((3.36 vs 1.97 \mu g/L; p = 0.10)\) and HAS group \((6.12 vs 2.83 \mu g/L; p = 0.04)\). Significant difference in NT-proBNP concentrations was found between those with and without septic shock in female patients \((2.42 [0.99–12.20] vs 12.53 \mu g/L [4.22–30.51 \mu g/L]; p = 0.014)\) (Fig. 1B), but not in all patients \((2.08 vs 4.64 \mu g/L; p = 0.10)\) or male patients \((1.96 [0.62–7.67] vs 3.36 \mu g/L [0.72–7.33 \mu g/L]; p = 0.53)\). Similarly, the difference in NT-proBNP concentrations was significant between nonintubated \((2.89 \mu g/L [0.69–8.72 \mu g/L])\) and intubated female patients \((7.00 \mu g/L [1.62–27.18 \mu g/L]; p = 0.041)\), but not in male patients \((2.08 \mu g/L [0.63–6.79] vs 3.36 \mu g/L [0.71–8.21 \mu g/L]; p = 0.14)\).

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

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 \(\mu g/L\), 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**<sup>a</sup> |       |                        |                                                               |
| 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)<sup>b</sup>                                  |
| 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.

<sup>a</sup>Patients 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.

<sup>b</sup>NT-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.
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
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 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 BNPs) 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          |             |
|---------------------------------|-----------------|-------------|-----------------|-------------|
|                                 | $r_s$           | $p$         | $n$             | $r_s$       | $p$         | $n$         | $P$         |
| 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| 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        | 91          | 0.8601      |
| 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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REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315:801–810
2. Rudd KE, Johnson SC, Aages KM, et al: Global, regional, and national sepsis incidence and mortality, 1990-2017: Analysis for the Global Burden of Disease Study. Lancet 2020; 395:200–211
3. Saito Y, Nakao K, Itoh H, et al: Brain natriuretic peptide is a novel cardiac hormone. Biochem Biophys Res Commun 1989; 158:360–368
4. Mukoyama M, Nakao K, Hosoda K, et al: Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J Clin Invest 1991; 87:1402–1412
5. Karjalainen AH, Ruskoaho H, Vuolteenaho O, et al: Effects of estrogen replacement therapy on natriuretic peptides and blood pressure. Maturitas 2004; 47:201–208
6. Bachmann KN, Huang S, Lee H, et al: Effect of testosterone on natriuretic peptide levels. J Am Coll Cardiol 2019; 73:1288–1296
7. Redfield MM, Rodeheffer RJ, Jacobsen SJ, et al: Plasma brain natriuretic peptide concentration: Impact of age and gender. J Am Coll Cardiol 2002; 40:976–982
8. Keyzer JM, Hoffmann JJ, Ringoir L, et al: Age- and gender-specific brain natriuretic peptide (BNP) reference ranges in primary care. Clin Chem Lab Med 2014; 52:1341–1346
9. Schröder J, Kahike V, Staubach KH, et al: Gender differences in human sepsis. Arch Surg 1998; 133:1200–1205
10. Tsang G, Insel MB, Weis JM, et al: Bioavailable estradiol concentrations are elevated and predict mortality in septic patients: A prospective cohort study. Crit Care 2016; 20:335
11. Witthaut R, Busch C, Fraunberger P, et al: Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: Impact of interleukin-6 and sepsis-associated left ventricular dysfunction. Intensive Care Med 2003; 29:1696–1702
12. Mokart D, Sannini A, Brun JP, et al: N-terminal pro-brain natriuretic peptide as an early prognostic factor in cancer patients developing septic shock. Crit Care 2007; 11:R37
13. Varpula M, Pulikki K, Karlsson S, et al; FINNSEPSIS Study Group: Predictive value of N-terminal pro-brain natriuretic peptide in severe sepsis and septic shock. Crit Care Med 2007; 35:1277–1283
14. Wang F, Wu Y, Tang L, et al: Brain natriuretic peptide for prediction of mortality in patients with sepsis: A systematic review and meta-analysis. Crit Care 2012; 16:R74
15. Papanikolaou J, Makris D, Mpaka M, et al: New insights into the mechanisms involved in B-type natriuretic peptide elevation and its prognostic value in septic patients. Crit Care 2014; 18:R94
16. Masson S, Caironi P, Fanizza C, et al: Sequential N-terminal pro-B-type natriuretic peptide and high-sensitivity cardiac troponin measurements during albumin replacement in patients with severe sepsis or septic shock. *Crit Care Med* 2016; 44:707–716

17. Khoury J, Arow M, Elias A, et al: The prognostic value of brain natriuretic peptide (BNP) in non-cardiac patients with sepsis, ultra-long follow-up. *J Crit Care* 2017; 42:117–122

18. Pandopatam G, Kashani K, Vallabhajosyula S: The role of natriuretic peptides in the management, outcomes and prognosis of sepsis and septic shock. *Rev Bras Ter Intensiva* 2019; 31:368–378

19. Rudiger A, Gasser S, Fischler M, et al: Comparable increase of B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide levels in patients with severe sepsis, septic shock, and acute heart failure. *Crit Care Med* 2006; 34:2140–2144

20. McLean AS, Huang SJ, Hyams S, et al: Prognostic values of B-type natriuretic peptide in severe sepsis and septic shock. *Crit Care Med* 2007; 35:1019–1026

21. Sturgess DJ, Marwick TH, Joyce C, et al: Prediction of hospital outcome in septic shock: A prospective comparison of tissue Doppler and cardiac biomarkers. *Crit Care* 2010; 14:R44

22. McLean AS, Huang SJ: Brain not processing: Is finding a role for BNP in sepsis like fitting a square peg into a round hole? *Crit Care* 2014; 18:161

23. Christ M, Laule-Kilian K, Hochholzer W, et al: Gender-specific risk stratification with B-type natriuretic peptide levels in patients with acute dyspnea: insights from the B-type natriuretic peptide for acute shortness of breath evaluation study. *J Am Coll Cardiol* 2006; 48:1808–1812

24. York MK, Gupta DK, Reynolds CF, et al: B-type natriuretic peptide levels and mortality in patients with and without heart failure. *J Am Coll Cardiol* 2018; 71:2079–2088

25. Custodero C, Wu Q, Ghita GL, et al: Prognostic value of NT-proBNP levels in the acute phase of sepsis on lower long-term physical function and muscle strength in sepsis survivors. *Crit Care* 2019; 23:230

26. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987; 40:373–383

27. Meyer B, Huelsmann M, Wexberg P, et al: N-terminal pro-B-type natriuretic peptide is an independent predictor of outcome in an unselected cohort of critically ill patients. *Crit Care Med* 2007; 35:2268–2273