Natriuretic Peptides to Predict Short-Term Mortality in Patients With Sepsis: A Systematic Review and Meta-analysis

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Abstract

Data are conflicting regarding the optimal cutoffs of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) to predict short-term mortality in patients with sepsis. We conducted a comprehensive search of several databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus) for English-language reports of studies evaluating adult patients with sepsis, severe sepsis, and septic shock with BNP/NT-proBNP levels and short-term mortality (intensive care unit, in-hospital, 28-day, or 30-day) published from January 1, 2000, to September 5, 2017. The average values in survivors and nonsurvivors were used to estimate the receiver operating characteristic curve (ROC) using a parametric regression model. Thirty-five observational studies (3508 patients) were included (median age, 51-75 years; 12%-74% males; cumulative mortality, 34.2%). A BNP of 622 pg/mL had the greatest discrimination for mortality (sensitivity, 0.695 [95% CI, 0.659-0.729]; specificity, 0.907 [95% CI, 0.810-1.003]; area under the ROC, 0.766 [95% CI, 0.734-0.797]). An NT-proBNP of 4000 pg/mL had the greatest discrimination for mortality (sensitivity, 0.728 [95% CI, 0.703-0.753]; specificity, 0.789 [95% CI, 0.710-0.867]; area under the ROC, 0.787 [95% CI, 0.766-0.809]). In prespecified subgroup analyses, identified BNP/NT-proBNP cutoffs had higher discrimination if specimens were obtained 24 hours or less after admission, in patients with severe sepsis/septic shock, in patients enrolled after 2010, and in studies performed in the United States and Europe. There was inconsistent adjustment for renal function. In this hypothesis-generating analysis, BNP and NT-proBNP cutoffs of 622 pg/mL and 4000 pg/mL optimally predicted short-term mortality in patients with sepsis. The applicability of these results is limited by the heterogeneity of included patient populations.

Sepsis continues to be a leading cause of mortality and morbidity in the United States and accounts for nearly $17 billion in annual health care expenditure.1 Sepsis is associated with multiorgan dysfunction, prominent among which are injury and dysfunction of the cardiovascular and renal systems.2,3 Cardiac dysfunction in patients with sepsis can manifest as a combination of circulatory failure, septic cardiomyopathy, and myocardial injury and refractory shock.1,4,13 With the development of sensitive laboratory technology, there is a renewed interest in the use of biomarkers for early and targeted treatment of cardiac dysfunction in patients with sepsis and septic shock.1 Cardiac biomarkers, such as cardiac troponin T, troponin I, B-type natriuretic peptide (BNP), and N-terminal pro-BNP (NT-proBNP), have been studied previously in patients with sepsis and septic shock.14,15 Prior studies have associated cardiac troponins with the degree of myocardial injury, hypotension, cardiomyopathy, and extent of vasopressor support.1,16 We previously reported that admission troponin T, but not serial troponin T, levels have been associated with in-hospital and long-term mortality in patients with sepsis.1

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meta-analysis evaluating troponins, Bessière et al14 documented that troponin levels correlated with shock severity and short-term and long-term mortality.

B-type natriuretic peptide is synthesized as a precursor protein (proBNP) in response to increased myocardial wall stress due to volume or pressure overload. Most of it is subsequently cleaved into active peptide BNP 1-32 and biologically inert NT-proBNP.17 Typically, NT-proBNP levels are higher than BNP levels.17,18 A 2012 meta-analysis found BNP as a predictor of mortality in patients with sepsis with pooled sensitivity and specificity of 79% and 60%; there was significant heterogeneity \( I^2 = 64\% \) among the evaluated studies.15 In this systematic analysis, BNP assays, clinical end points, and vasopressor use varied markedly among the enrolled studies.15 In other critically ill patients with pulmonary embolism, chronic obstructive pulmonary disease, and congestive heart failure, BNP has been strongly associated with clinical outcomes and has been incorporated into risk stratification.19-21 In patients with sepsis, however, there are conflicting data on the role of BNP/NT-proBNP as a risk-stratification and prognostication tool. Some investigators have considered BNP as a marker of severity, whereas others have reported it as an independent prognostic test. In light of the multiple recent studies with contrasting results, we sought to undertake a systematic review and meta-analysis of natriuretic peptide levels in the prognostication of patients with sepsis and septic shock.22-29 These discrepant results may be partly due to the heterogeneity of sepsis, differences in timing of BNP measurement, types of assays used, small sample sizes, and lack of control for septic cardiomyopathy.28,29 The primary outcome was to develop a summative value of BNP and NT-proBNP that is associated with mortality in this population.

**PATIENTS AND METHODS**

**Data: Sources, Strategies, and Inclusion**

We conducted a comprehensive search of several databases for articles published from January 1, 2000, to September 5, 2017. The databases included Ovid MEDLINE Epub Ahead of Print, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by a medical librarian with input from the authors. Controlled vocabulary supplemented with keywords was used to search for mortality prediction in patients with sepsis using BNP or NT-proBNP in adults (Supplemental Appendix 1, available online at http://mcpiqournal.org). The abstracts were screened by 2 independent reviewers (Saarwaani Vallabhajosyula, Shashaank Vallabhajosyula). All references of included studies were evaluated for additional studies. Study inclusion was based on the consensus of the 2 reviewers. A third independent reviewer (P.R.S.) served as the referee in cases of disagreement between the first 2 reviewers. The search strategy and reporting were performed following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.31 This protocol has not been registered previously in available systematic review databases. Corresponding authors of included studies were not contacted for patient-level data, and all analyses performed in this study were based on the summative publicly available data. A subsequent updated search was performed between September 5, 2017, and June 25, 2019, and the results are presented in Supplemental Appendix 2 and Supplemental Table 1 (available online at http://mcpiqojournal.org). These studies were not included in the final meta-analysis for this study.

English-language studies evaluating adult patients (>18 years) with sepsis, severe sepsis, or septic shock defined using either the 2001 International Sepsis Definitions or Sepsis-3

**ARTICLE HIGHLIGHTS**

- B-type natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP) levels are often elevated in patients with sepsis.
- The optimal cutoffs for mortality prediction remain incompletely understood.
- BNP and NT-proBNP levels of 622 pg/mL and 4000 pg/mL predicted short-term mortality.
(Third International Consensus Definitions for Sepsis and Septic Shock)³³ criteria were included. Human studies of case-control, cohort, and randomized trial study designs were included. Short-term mortality was defined as intensive care unit mortality, in-hospital mortality, 28-day mortality, or 30-day mortality. In studies evaluating unselected critically ill patients, only studies for which a 2×2 table could be constructed between BNP/NT-proBNP levels and mortality were included. Abstracts that were not published in full text were excluded. Studies designed as case reports/series, systematic or narrative reviews, pediatric or animal studies, and studies without relevant outcomes were excluded. If multiple studies were published by the same group of authors over the same study duration, only a single study with relevant outcomes was included. Data abstracted included study year, population, location, type of study, comorbidities, and clinical outcomes. The clinical outcome of interest was BNP/NT-proBNP level that was associated with mortality.

Evidence Synthesis
The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale for nonrandomized studies by 2 independent reviewers (Saarwaani Vallabha-josyula, Shashaank Vallabhajosyula) (Supplemental Table 2, available online at http://mcpiqojournal.org) (Cohen κ statistic for agreement between reviewers, 0.82).³⁴ This scale involves evaluation based on 3 areas: (1) selection of the study groups, (2) comparability among groups, and (3) the assessment of outcome between the groups. We extracted or calculated the average values of BNP and NT-proBNP tests for those who survived and those who died. We then estimated the receiver operating characteristic curve (ROC) using the parametric ROC.
| Natriuretic peptide | Reference, year | Country | Setting       | Study design     | Inclusion criteria                      | Exclusion criteria                                      |
|---------------------|----------------|---------|---------------|-----------------|-----------------------------------------|---------------------------------------------------------|
| BNP                 | Charpentier et al., 2004 | France | Single ICU & center | Prospective cohort | Sepsis | Pregnancy, CHF, HTN, LVH, CP, COPD, CKD |
| BNP                 | Cuthbertson et al., 2005 | Scotland | Single ICU & center | Prospective cohort | Sepsis | Severe neurologic injury |
| BNP                 | Issa et al., 2008 | Brazil | Single ICU & center | Prospective cohort | Severe sepsis and septic shock | ICH, hemodialysis, heart disease, ACS |
| BNP                 | Klouche et al., 2014 | France | Single ICU & center | Prospective cohort | Severe sepsis and septic shock | Pregnancy, age < 18 y, CHF, RWMA, CKD, acute VTE |
| BNP                 | Li et al., 2016 | China | Single ICU & center | Prospective cohort | Severe sepsis and septic shock | Age < 18 y, CHF, CKD, ICU stay < 24 h, immunosuppression |
| BNP                 | Liu et al., 2016 | China | Single ICU & center | Prospective cohort | Surgical sepsis | Transplant, cardiac surgery, immunosuppression |
| BNP                 | McCormack et al., 2007 | Australia | Single ED & center | Retrospective cohort | Sepsis | NA |
| BNP                 | McLean et al., 2007 | France | Single ICU & center | Prospective cohort | Severe sepsis and septic shock | Negative cultures, poor echo windows |
| BNP                 | Papanikolaou et al., 2014 | Greece | Single ICU & center | Prospective cohort | Severe sepsis/septic shock, IMV | CHF, CKD, PH, CNS disease, inotropes use |
| BNP                 | Post et al., 2008 | Germany | Single ICU & center | Prospective cohort | Septic shock | CHF |
| BNP                 | Ryoo et al., 2015 | Korea | Single ICU & center | Prospective cohort | Septic shock | MI, CHF |
| BNP                 | Salim et al., 2015 | Egypt | Single ICU & center | Prospective cohort | Sepsis, severe sepsis, septic shock | Coronary artery disease, CHF, atrial fibrillation |
| BNP                 | Shor et al., 2006 | Israel | Single ICU & center | Prospective cohort | Sepsis, septic shock | CHF, ACS, CKD, VTE, COPD, cancer |
| BNP                 | Sturgess et al., 2010 | Australia | Single ICU & center | Prospective cohort | Septic shock | VHD |
| BNP                 | Turner et al., 2011 | US | Single ICU & center | Prospective cohort | Sepsis, severe sepsis, septic shock | Organ transplant |
| BNP                 | Yucel et al., 2008 | Turkey | Single ICU & center | Prospective cohort | Sepsis | Cardiogenic shock, trauma, burns |
| NT-proBNP           | Balcan et al., 2012 | Turkey | Single ICU & center | Prospective cohort | Sepsis | CKD, AKI |
| NT-proBNP           | Balcan et al., 2015 | Turkey | Single ICU & center | Prospective cohort | Sepsis | NA |
| NT-proBNP           | Brueckmann et al., 2005 | Germany | Multiple ICUs & centers | Prospective cohort | Sepsis | DCM, CP, VHD, CKD, ACS |
| NT-proBNP           | Cheng et al., 2015 | China | Single ICU & center | Prospective cohort | Sepsis | Age < 65 y, ICU stay < 4 h, ACS, VHD, COPD, CKD, immunosuppression |
| NT-proBNP           | García Villalba et al., 2017 | Spain | Single ICU & center | Prospective cohort | Sepsis | NA |

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| Natriuretic peptide | Reference, year | Country | Setting | Study design | Inclusion criteria | Exclusion criteria |
|---------------------|----------------|---------|---------|--------------|------------------|-------------------|
| NT-proBNP           | Guaricci et al, 2015 | Italy | Single ICU & center | Prospective cohort | Sepsis | LVEF <50%, DCM, CP, VHD, CKD, TBI, death <72 h |
| NT-proBNP           | Ju et al, 2012 | China | Single ICU & center | Prospective cohort | Sepsis | Pregnancy, CHF, age <18 y, CKD |
| NT-proBNP           | Landesberg et al, 2012 | Israel | Single ICU & center | Prospective cohort | Severe sepsis and septic shock | VHD, RWMA, MI, poor echo images |
| NT-proBNP           | Li et al, 2014 | China | Single ICU & center | Prospective cohort | Sepsis | Age <18 y, cancer, ACS, CKD, ICU stay <24 h |
| NT-proBNP           | Mokart et al, 2007 | France | Single ICU & center | Prospective cohort | Sepsis | CHF, CKD, COPD, brain disorders |
| NT-proBNP           | Park et al, 2011 | Korea | Single ICU & center | Prospective cohort | Septic shock, ARDS | CNS disease, pregnancy, MI, CHF, CKD, VTE |
| NT-proBNP           | Roch et al, 2005 | France | Single ICU & center | Prospective cohort | Septic shock, IMV | CHF, COPD, CKD, CNS disease |
| NT-proBNP           | Sasko et al, 2015 | Germany | Single ICU & center | Prospective cohort | Septic shock | ARDS |
| NT-proBNP           | Sekino et al, 2017 | Japan | Single ICU & center | Prospective cohort | Septic shock | Intestinal ischemia/resection |
| NT-proBNP           | Sturgess et al, 2010 | Australia | Single ICU & center | Prospective cohort | Septic shock | VHD |
| NT-proBNP           | Varpula et al, 2007 | Finland | Multiple ICUs & centers | Prospective cohort | Sepsis, septic shock | CHF, CAD, prior MI, HTN, diabetes mellitus |
| NT-proBNP           | Wang et al, 2016 | China | Single ICU & center | Prospective cohort | Sepsis | ACS, CHF, CAD, hepatic/renal failure |
| NT-proBNP           | Wang et al, 2015 | China | Single ICU & center | Prospective cohort | Septic shock | Stay <72 h, prior MI, CNS disease |
| NT-proBNP           | Zhang et al, 2013 | China | Single ED & center | Prospective cohort | Sepsis | CHF, DCM, VHD, ACS, CKD |

ACS = acute coronary syndrome; AKI = acute kidney injury; ARDS = acute respiratory distress syndrome; BNP = B-type natriuretic peptide; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; CP = cor pulmonale; DCM = dilated cardiomyopathy; echo = echocardiography; ED = emergency department; HTN = hypertension; ICH = intracranial hemorrhage; ICU = intensive care unit; IMV = invasive mechanical ventilation; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MI = myocardial infarction; NA = not available; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PH = pulmonary hypertension; RWMA = regional wall motion abnormalities; TBI = traumatic brain injury; US = United States; VHD = valvular heart disease; VTE = venous thromboembolism.
| Natriuretic peptide | Author/Year | Total patients | Age (years) | Male sex | BNP/NT-proBNP assay | BNP/NT-proBNP timing |
|---------------------|-------------|----------------|-------------|----------|---------------------|---------------------|
| BNP                 | Charpentier 2004 | 34  | 56 (2.7) | 16 (47.1) | Shionora-BNP immunoradiometric assay | Days 1, 2, 3, 4, 8 |
| BNP                 | Cuthbertson 2005 | 35  | 66 (55-74) | 20 (57) | Bayer ADVIA Immunoassay | ICU admission |
| BNP                 | Issa 2008     | 23  | 51.3 (18.6) | 14 (60.9) | Microparticle Immunoassay (MEIA-Abbott) | ICU admission |
| BNP                 | Klouche 2014  | 47  | 60 (16) | 27 (57.5) | Immunochemiluminescent Access 2 analyzer | Day 5 |
| BNP                 | Li 2016       | 84  | NA       | 56 (66.7) | Elecsys 2010 Roche Diagnostics | Days 1, 3, 5 |
| BNP                 | Liu 2016      | 156 | 61 (40-76) | 100 (64.4) | NA | ICU admission |
| BNP                 | McCormack 2016 | 37  | NA       | NA       | NA | ED admission |
| BNP                 | McLean 2007   | 40  | NA       | NA       | Triage BNP detector | Days 1-10 |
| BNP                 | Papanikolaou 2014 | 42  | NA       | 26 | Biosite Triage BNP meter | Days 1, 2, 3, 4, 5 |
| BNP                 | Post 2008     | 93  | 65 (53-73.5) | 51 (55) | Biosite Triage BNP meter | Day 5 |
| BNP                 | Ryoo 2015     | 290 | 63.9 (13) | 170 (58.6) | ADVIA Centaur; Bayer Diagnostics | ICU admission |
| BNP                 | Salim 2015    | 40  | NA       | 22 | Enzyme immunoassay | Days 1, 3 |
| BNP                 | Shor 2006     | 21  | 79.3 (9.15) | NA | Axsym Abbott immunoassay | ICU admission |
| BNP                 | Sturgess 2010 | 21  | 53.5 (19.6) | 13 (61.9) | Biosite Triage BNP analyzer | <72 hours |
| BNP                 | Turner 2011   | 231 | 59 (3) | 100 (43) | — | — |
| BNP                 | Yucel 2008    | 40  | NA       | NA | Shionora-BNP assay, Cisbio International | Days 1, 2, 28 |
| BNP                 | Zhang 2012    | 73  | 59 (16) | 43 (64.2) | Biosite Triage BNP analyzer | ICU admission |
| NT-proBNP           | Balcan 2016   | 48  | 66.8 (17.9) | 74 (52.5) | NA | ICU admission |
| NT-proBNP           | Balcan 2015   | 141 | 61.5 (12.4) | 20 (42) | NA | <24 hours |
| NT-proBNP           | Brueckmann 2005 | 57  | 55 (16.3) | 42 (74) | Biozol, Enzyme Immunoassay | Day 2 |
| NT-proBNP           | Cheng 2015    | 430 | 74.15 (14) | 219 (50.8) | NA | ICU admission |
| NT-proBNP           | Garcia 2017   | 174 | 73 (16) | 102 (58.6) | LOCI Chemiluminescent Immunoassay | ICU admission |
| NT-proBNP           | Guaricci 2015 | 40  | 64 (48.75-72) | 22 (55) | Biozol, Enzyme Immunoassay | 6, 72 hours |
| NT-proBNP           | Ju 2012       | 100 | 65.97 (13.95) | 74 (74) | Cobase 411, Roche Diagnostics | ICU admission |
| NT-proBNP           | Landesberg 2012 | 262 | NA | 159 (60.7) | Elecsys 2010 Roche Diagnostics | ICU admission |
| NT-proBNP           | Li 2014       | 102 | 63 (21) | 49 (48) | Elecsys 2010 Roche Diagnostics | Days 1, 3, 5 |
| NT-proBNP           | Mokart 2007   | 51  | 56 (50-68) | 32 (62) | Roche Elecsys 2010 | Day 1, 2 |
| NT-proBNP           | Park 2011     | 49  | 64 (15) | 28 (57.1) | Elecsys 2010 Roche Diagnostics | Days 1, 2, 3 |
| NT-proBNP           | Roch 2005     | 39  | 63 (12) | NA | Elecsys 2010 Roche Diagnostics | ICU admission |
| NT-proBNP           | Sasko 2015    | 52  | 71.4 (8.5) | 31 (59.6) | NA | ICU admission |
| NT-proBNP           | Sekino 2017   | 57  | 71 (62-79) | 35 (61) | Elecsys 2010 Roche Diagnostics | ICU admission |
| NT-proBNP           | Sturgess 2010 | 21  | 53.5 (19.6) | 13 (61.9) | Elecsys 2010 Roche Diagnostics | <72 hours |

**TABLE 2. Study Population and Natriuretic Peptide Characteristics**

Continued on next page
regression model proposed by Alonzo and Pepe. Each study was weighted by the number of patients. We used the area under the ROC (AUROC) as a measure of test performance for mortality prediction. Optimal sensitivity (Sn) and specificity (Sp) and corresponding cutoffs were estimated using the Youden index. Multiple subgroup analyses were performed to confirm the primary findings and to understand the predictive capacity of BNP/NT-proBNP. Subgroups were stratified by timing of BNP/NT-proBNP measurement (≤24 hours/>24 hours after hospital admission), study era (≤2010/>2010), studies performed in the United States and Europe vs other countries, and studies evaluating all types of sepsis vs only severe sepsis and septic shock. All statistical analyses were conducted using Stata statistical software, version 15.1 (StataCorp).

RESULTS
A total of 452 unique studies were identified by the initial search strategy. Abstracts and subsequently full texts of selected articles were screened, and 35 studies, with a total of 3508 patients, were selected for data extraction (Figure 1). All the studies were of moderate methodological quality. Detailed study characteristics and populations are highlighted in Table 1. Concomitant heart failure, cor pulmonale, valvular heart disease, acute coronary syndrome, intracranial hemorrhage, and chronic kidney disease were the most common reasons for exclusion of patients across the 36 studies. The median age across the studies varied from 51 to 75 years, and 12% to 74% of patients were male. Most studies measured BNP/NT-proBNP at emergency department or intensive care unit admission or within the first 24 hours after admission (Table 2).

Absolute mortality rate was not reported in one study. Cumulative short-term mortality was 34.2% (1188/3471) in the 35 studies.
| Natriuretic peptide | Reference, year | Total patients | Patients alive | Patients dead | Mortality prediction |
|---------------------|-----------------|----------------|---------------|---------------|---------------------|
|                     | No. Mean ± SD or median (IQR) | | No. Mean ± SD or median (IQR) | | Cutoff Sn/Sp (%) AUROC |
| BNP                 | Charpentier et al, 2004 | 34 24 | 181±46 | 246 | 190 70/67 0.66 |
| BNP                 | Cuthbertson et al, 2005 | 35 25 | 651 (242-1023) | 377 (85-683) | 100 NA NA |
| BNP                 | Issa et al, 2008 | 23 8 | 173±1.8 | 195.5±2.7 | NA NA NA |
| BNP                 | Klouche et al, 2014 | 47 34 | 836±859 | 2605±1957 | NA NA NA |
| BNP                 | Li et al, 2016 | 84 40 | 216 (110-689) | 456.7 (211-1024.2) | NA NA NA |
| BNP                 | Liu et al, 2016 | 156 110 | 500 (171-1689) | 3763 (628-23,382) | NA NA NA |
| BNP                 | McCormack et al, 2016 | 37 NA | 767.1±315.37 | 1294±946.84 | NA NA NA |
| BNP                 | McLean et al, 2007 | 40 31 | 603±708 | 788±904 | NA NA NA |
| BNP                 | Papanikolaou et al, 2014 | 42 22 | 732±122.5 | 1099.5±133.8 | 800 65/64 0.7 |
| BNP                 | Post et al, 2008 | 93 55 | 119 (79.5-652) | 672 (122-779.3) | 121 76/52.7 0.65 |
| BNP                 | Ryoo et al, 2015 | 290 227 | 469±761.8 | 1156±1425.3 | NA NA NA |
| BNP                 | Salm et al, 2015 | 40 23 | 326±199.1 | 622±157.4 | 449 94/79 0.88 |
| BNP                 | Shor et al, 2006 | 21 13 | 121±368.9 | 201±301.6 | NA NA NA |
| BNP                 | Sturgess et al, 2010 | 21 15 | 448±607 | 1289±1155 | 254 83/60 0.76 |
| BNP                 | Tucker et al, 2011 | 231 160 | 309±61 | 986±312 | NA NA NA |
| BNP                 | Yucel et al, 2008 | 40 20 | 13.72±12.95 | 254.78±308.62 | 32.1 100/95 0.99 |
| BNP                 | Zhang et al, 2012 | 73 40 | 550 (331-788) | 738 (596-937) | 816 48/87.5 0.71 |
| BNP                 | Balcan et al, 2016 | 48 33 | 1882±1652.29 | 12,202±12,567.84 | 3736 NA 0.703 |
| BNP                 | Balcan et al, 2015 | 141 69 | 3726 | 10,428 | NA NA NA |
| NT-proBNP           | Brueckmann et al, 2005 | 57 41 | 493 (314-1126) | 1431 (712-1920) | 1400 50/90.2 0.68 |
| NT-proBNP           | Cheng et al, 2015 | 430 294 | 2170±625.28 | 5873±1768.37 | 4542 68/95 0.62 |
| NT-proBNP           | García Villalba et al, 2017 | 174 157 | 1112 (379-2570) | 6187 (1780-9949) | 1330 NA 0.793 |
| NT-proBNP           | Guaricci et al, 2015 | 40 18 | 6586 (3281-9573) | 12,743 (8352-14,289) | 1000 NA 0.73 |
| NT-proBNP           | Ju et al, 2012 | 100 67 | 2902.23±506.08 | 3239±2687.31 | NA NA NA |
| NT-proBNP           | Landesberg et al, 2012 | 262 167 | 2275 (567-9426) | 13,980 (5877-34,718) | NA NA NA |
| NT-proBNP           | Li et al, 2014 | 102 60 | 360.4 (178-15-1204.5) | 539 (314.5-785.4) | NA NA NA |
| NT-proBNP           | Mokart et al, 2007 | 51 19 | 3414 (754-9005) | 7939 (4495-33,662) | 6624 86/77 0.87 |
| NT-proBNP           | Park et al, 2011 | 49 18 | 4000 (1614-11,233) | 2819 (937-12,256) | NA 82/81 0.82 |
| NT-proBNP           | Roch et al, 2005 | 39 17 | 7856 (1291-12972) | 34,028 (11,735-49,320) | 13,600 73/83 0.8 |
| NT-proBNP           | Sasaki et al, 2015 | 52 24 | 1177±1854 | 8623±34,296 | NA NA NA |
| NT-proBNP           | Sekino et al, 2017 | 57 44 | 8710 (1903-17,930) | 34,820 (5432-65,122) | NA NA NA |
| NT-proBNP           | Sturgess et al, 2010 | 21 15 | 841±818 | 1801±853 | 400 83/40 0.67 |

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that reported mortality rates. Detailed mortality rates and BNP/NT-proBNP values based on the vital status of patients in each study are reported in Table 3. As noted in Table 3, studies reported varying cutoffs of BNP/NT-proBNP in estimating mortality in patients with sepsis and septic shock. These cutoffs had varying AUROCs of 0.62 to 0.99 in the studies that reported these statistics. Using the parametric ROC regression model, we estimated the AUROC for BNP and NT-proBNP individually (Figures 2A and B). A BNP value of 622 pg/mL (to convert to ng/L, multiply by 1.0) had the greatest discrimination for short-term mortality prediction in patients with sepsis—Sn, 0.695 (95% CI, 0.659-0.729); Sp, 0.907 (95% CI, 0.810-1.003); and AUROC, 0.766 (95% CI, 0.734-0.797). An NT-proBNP value of 4000 pg/mL (1 pg/mL = 0.118 pmol/L) had the greatest discrimination for short-term mortality prediction in patients with sepsis—Sn, 0.728 (95% CI, 0.703-0.753); Sp, 0.789 (95% CI, 0.710-0.867); and AUROC, 0.787 (95% CI, 0.766-0.809). In the prespecified subgroup analyses, the BNP cutoff had greater discrimination for in-hospital mortality when measured 24 hours or less after hospital admission—AUROC, 0.920 (95% CI, 0.889-0.951); Sn, 0.779 (95% CI, 0.723-0.834); and Sp, 0.986 (95% CI, 0.966-1.000), as compared to more than 24 hours after hospital admission—AUROC, 0.725 (95% CI, 0.684-0.766); Sn, 0.644 (95% CI, 0.599-0.688); and Sp, 0.964 (95% CI, 0.892-1.000). Because only a limited number of studies measured NT-proBNP during the first 24 hours, this subgroup analysis was restricted to more than 24 hours after hospital admission. The NT-proBNP values measured at more than 24 hours after hospital admission had an AUROC of 0.790 (95% CI, 0.768-0.812), Sn of 0.736 (95% CI, 0.711-0.761), and Sp of 0.773 (95% CI, 0.690-0.857). When stratified by year, BNP (≤2010—AUROC of 0.77 [95% CI, 0.73-0.80], Sn of 0.67 [95% CI, 0.58-0.75], and Sp of 0.59 [95% CI, 0.50-0.67]; >2010—AUROC of 0.82 [95% CI, 0.78-0.85], Sn of 0.76 [95% CI, 0.73-0.80], and Sp 0.93 [95% CI, 0.82-1.00]) and NT-proBNP (≤2010—AUROC of 0.78 [95% CI, 0.63-0.84], Sn of 0.64 [95% CI, 0.57-0.71], and Sp of 0.99 [95% CI, 0.99-1.00];
>2010—AUROC of 0.81 [95% CI, 0.78-0.83], Sn of 0.73 [95% CI, 0.70-0.76], and Sp 0.83 [95% CI, 0.76-0.89]) had greater accuracy for studies performed after 2010. When restricted to only patients with severe sepsis/septic shock, BNP had higher discrimination (severe sepsis/septic shock—AUROC of 0.79 [95% CI, 0.75-0.84], Sn of 0.70 [95% CI, 0.65-0.73], and Sp of 0.83 [95% CI, 0.73-0.94]; all sepsis—AUROC of 0.77 [95% CI, 0.72-0.82], Sn of 0.71 [95% CI, 0.66-0.76], and Sp of 0.92 [95% CI, 0.74-1.00]), but NT-proBNP had lower discrimination (severe sepsis/septic shock—AUROC of 0.80 [95% CI, 0.77-0.84], Sn of 0.66 [95% CI, 0.62-0.71], and Sp of 0.93 [95% CI, 0.87-0.98]; all sepsis—AUROC of 0.84 [95% CI, 0.82-0.87], Sn of 0.74 [95% CI, 0.70-0.77], and Sp of 0.87 [95% CI, 0.82-0.87]).

When stratified by country, studies performed in the United States and Europe had greater accuracy for mortality prediction for both BNP (United States/Europe—AUROC of 0.82 [95% CI, 0.77-0.87], Sn of 0.70 [95% CI, 0.64-0.77], and Sp of 0.86 [95% CI, 0.77-0.95]; other countries—AUROC of 0.75 [95% CI, 0.71-0.79], Sn of 0.70 [95% CI, 0.65-0.74], and Sp of 0.92 [95% CI, 0.75-1.00]) and NT-proBNP (United States/Europe—AUROC of 0.83 [95% CI, 0.78-0.87], Sn of 0.70 [95% CI, 0.65-0.76], and Sp of 0.98 [95% CI, 0.94-1.00]; other countries—AUROC of 0.78 [95% CI, 0.76-0.81], Sn of 0.71 [95% CI, 0.68-0.74], and Sp of 0.79 [95% CI, 0.71-0.87]).

DISCUSSION

In this systematic review and meta-analysis of 36 studies and 3508 patients, we noted that (1) sepsis continues to be associated with a high mortality of 34.2%, (2) BNP and NT-proBNP are frequently elevated in patients with sepsis and are prognostic in this population, and (3) optimal cutoffs for BNP and NT-proBNP were calculated at 622 pg/mL and 4000 pg/mL for prediction of short-term mortality in patients with sepsis and septic shock. In prespecified subgroup analyses, identified BNP/NT-proBNP cutoffs had higher discrimination if specimens were obtained 24 hours or less after admission, in patients with severe sepsis/septic shock, in patients enrolled after 2010, and in studies performed in the United States and Europe.

The release of BNP and NT-proBNP in patients with sepsis is stimulated by myocytic stretch with ventricular dysfunction and proinflammatory molecules such as lipopolysaccharide, interleukin 1, C-reactive protein, and cardiotrophin 1 promoting BNP gene expression and release. Furthermore, concomitant renal failure and processes of care such as catecholamine infusions and volume resuscitation lead to an elevation in BNP/NT-proBNP levels independent of ventricular function. Importantly, the timing of BNP
release and therefore the optimal timing of measurement in this critically ill population remains debatable. As noted in this meta-analysis, there was wide variation in the timing of BNP measurement. Most studies measured it at admission or within the first 24 hours, which is reflective of contemporary clinical practice. It is important to note that in patients with sepsis, adequate fluid resuscitation and hemodynamic restoration can result in unmasking of left ventricular systolic dysfunction as manifested by a decrease in ejection fraction within the first 72 hours. Serial BNP testing may have greater clinical utility in prognostication for patients with sepsis than a 1-time measurement. Papanikolou et al recently reported that a persistently elevated BNP level of greater than 500 pg/mL was a better predictor of 28-day mortality than isolated BNP values. Inability to reduce BNP to less than 500 pg/mL predicted 28-day mortality with an AUROC of 0.74 (95% CI, 0.55-0.93; P=.03). In our meta-analysis, we were unable to assess the utility of serial BNP testing in mortality prediction because of high heterogeneity in the timing and frequency of sampling.

The use of natriuretic peptides to evaluate cardiac function in patients with sepsis has been studied extensively in multiple studies, including studies included in this meta-analysis. However, the evaluation of cardiac function with BNP has to be balanced against the potential confounding from respiratory pathology and renal failure. Pulmonary pathology such as acute respiratory distress syndrome and chronic obstructive pulmonary disease and interventions such as mechanical ventilation influence the BNP levels in this population. As noted in this meta-analysis, studies variably exclude preexisting chronic kidney disease and inconsistently adjust for acute kidney injury in their analyses. In patients with sepsis, studies have found conflicting results regarding correlations between BNP and serum creatinine levels. In an updated search incorporating studies from 2017-2019, there were no changes in the profile or outcome prediction using BNP/NT-proBNP. Further studies are needed to develop clinically relevant BNP cutoffs stratified by renal function in patients with sepsis to more usefully define ranges of BNP in these patients. Lastly, BNP/NT-proBNP needs to be contextualized to age and sex. Cutoffs based on age and sex have been suggested in primary care patients and heart failure populations but have not been validated in patients with sepsis at the current time.

It is important to note that unlike in patients with heart failure, there are no current cutoffs for BNP/NT-proBNP in patients with sepsis. Using a large sepsis population, we were able to develop cutoffs for mortality prediction in this population. It is important that biomarkers be considered in prognosticating modeling and early prediction of outcomes. A combination of early measurement of cardiac biomarkers has been postulated to differentiate Takotsubo cardiomyopathy from acute myocardial infarction. Similar paradigms might be useful in predicting the extent of reversible myocardial dysfunction and long-term risk for heart failure in patients with sepsis and septic cardiomyopathy. Furthermore, the use of cardiac biomarkers in risk scoring systems is worthy of further study. Khoury et al found the BNP level at admission to be more predictive of short-term mortality than the Sequential Organ Failure Assessment score. In contrast, Ryoo et al reported that the combination of BNP with the Sequential Organ Failure Assessment score resulted in better prognostication in patients with sepsis than either method alone. The use of cardiac biomarkers, including BNP/NT-proBNP, may be of incremental benefit in improving the accuracy of cardiovascular dysfunction in this population that may aid in personalized therapies for sepsis. The BNP and NT-proBNP levels of 622 pg/mL and 4000 pg/mL noted in our study need further validation in carefully designed prospective studies. Given the subgroup analyses performed in our study, inclusion of pertinent enriched populations might aid in development of studies with a pragmatic sample size.

This study has important limitations. The selection of all types of sepsis can cause substantial heterogeneity in the assessment of clinical outcomes. Importantly, sepsis and septic shock may be fundamentally different in their etiology and clinical course. Furthermore, most studies did not systematically evaluate cardiac dysfunction. As we have reported previously, cardiac
dysfunction and injury as measured by echocardiography or cardiac troponin T levels are associated with worse outcomes.\textsuperscript{1,3-5,7,9} Fluid balance, prior heart failure, use of inotropic medications, and acute septic cardiomyopathy are closely associated with BNP release, and age, sex, and renal function are associated with varying BNP degradation.\textsuperscript{74} However, these factors were not systematically assessed in the individual studies included in our analyses, limiting the generalizability of our findings. Our study consisted primarily of observational studies, which have their own limitations. Observational studies are prone to confounding by indication and heterogeneity. This meta-analysis was performed in a study-level population, and thus, despite best attempts, crucial differences in patient characteristics across studies may have contributed to the results we observed. In addition, it is clear that natriuretic peptide assays vary substantially in their dynamic ranges. Thus, different assays may provide different numerical results in studies. Unfortunately, the data did not allow us to separate out those studies. It is clear, for this reason alone but likely for others as well, that a heterogeneity analysis would not have been productive.\textsuperscript{17,25} Finally, this study evaluated short-term mortality only, with limited insight into long-term survival and functional recovery, both of which remain a challenge in patients with sepsis and cardiac dysfunction.\textsuperscript{4}

**CONCLUSION**

In this hypothesis-generating meta-analysis of 3508 patients, BNP and NT-proBNP levels of 622 pg/mL and 4000 pg/mL were noted to predict short-term mortality with an AUROC of 0.766 and 0.787, respectively. Further dedicated research into the incorporation of these biomarkers into prognostic models and structured evaluation of cardiovascular dysfunction in patients with sepsis are needed to understand the clinical implications of these findings.

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**SUPPLEMENTAL ONLINE MATERIAL**

Supplemental material can be found online at http://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Abbreviations and Acronyms:** AUROC = area under the receiver operating characteristic curve; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; ROC = receiver operating characteristic curve; Sn = sensitivity; Sp = specificity

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