Diagnostic and prognostic utilities of multimarkers approach using procalcitonin, B-type natriuretic peptide, and neutrophil gelatinase-associated lipocalin in critically ill patients with suspected sepsis

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Abstract

Background: We investigated the diagnostic and prognostic utilities of procalcitonin (PCT), B-type natriuretic peptide (BNP), and neutrophil gelatinase-associated lipocalin (NGAL) in critically ill patients with suspected sepsis, for whom sepsis was diagnosed clinically or based on PCT concentrations.

Methods: PCT, BNP, and NGAL concentrations were measured in 340 patients and were followed up in 109 patients. All studied biomarkers were analyzed according to the diagnosis, severity, and clinical outcomes of sepsis.

Results: Clinical sepsis and PCT-based sepsis showed poor agreement (kappa = 0.2475). BNP and NGAL showed significant differences between the two groups of PCT-based sepsis (P = 0.0001 and P < 0.0001), although there was no difference between the two groups of clinical sepsis. BNP and NGAL were significantly different according to the PCT staging and sepsis-related organ failure assessment subscores (P < 0.0001, all). BNP and PCT concentrations were significantly higher in the non-survivors than in the survivors (P = 0.0002) and showed an equal ability to predict in-hospital mortality (P = 0.0001). In the survivors, the follow-up NGAL and PCT concentrations were significantly lower than the initial values (148.7 ng/mL vs. 214.5 ng/mL, P < 0.0001; 0.61 ng/mL vs. 5.56 ng/mL, P = 0.0012).

Conclusions: PCT-based sepsis diagnosis seems to be more reliable and discriminating than clinical sepsis diagnosis. Multimarker approach using PCT, BNP, and NGAL would be useful for the diagnosis, staging, and prognosis prediction in the critically ill patients with suspected sepsis.

Keywords: B-type natriuretic peptide, Neutrophil gelatinase-associated lipocalin, Procalcitonin, Sepsis, Diagnosis, Prognosis

Background

Sepsis is a systemic inflammatory response caused by infection. Progression to severe sepsis and septic shock is one of the main causes of high morbidity and mortality in critically ill patients in emergency or intensive care settings [1,2]. Since prompt and specific treatment in the patients with severe sepsis and septic shock has shown improved outcomes, it is crucial to ensure a timely diagnosis of this disease progression [3,4]. The sepsis-related organ failure assessment (SOFA) score has been used to describe and evaluate organ dysfunctions and failures in these patients [5].

Procalcitonin (PCT) has been extensively studied in various clinical settings, and growing evidences support its potential ability to diagnose sepsis, estimate its severity, and provide a prognosis [6-8]. Regarding organ dysfunctions and failures, various novel biomarkers have shown promise in clinical practice. B-type natriuretic peptide...
peptide (BNP) has been used to successfully aid in the diagnosis of heart failure, and its concentrations correlated with both disease severity and prognosis [9-11]. Neutrophil gelatinase-associated lipocalin (NGAL) has been regarded as a sensitive, specific, and early predictive biomarker for acute kidney injury (AKI) [12-14]. In a recent meta-analysis, one of the major findings was that 41% of patients diagnosed with AKI would have been missed by creatinine alone [13].

A few recent studies reported a combined use of these novel biomarkers [15,16]. In a multicenter prospective study (GALLANT trial), the combination of plasma NGAL and BNP demonstrated clinical implications for risk stratification in the patients with acute heart failure, and plasma NGAL at discharge was a strong indicator of adverse outcomes [15]. Our previous study showed the diagnostic utility of plasma NGAL for AKI in the critically ill patients with suspected sepsis, for whom PCT was used for the diagnosis and staging of sepsis [16]. If several biomarkers, a marker for sepsis and respective markers for each organ dysfunction, are combined together, it will provide more objective and reliable guide for the diagnosis, risk stratification, prognosis, and treatment of sepsis. In the present study, we wanted to explore the diagnostic and prognostic utilities of PCT, BNP, and NGAL in critically ill patients with suspected sepsis, for whom sepsis was diagnosed clinically or based on PCT concentrations.

Methods
Study population
A prospective, observational study was conducted in two university hospitals: a 400-bed hospital (Sant’ Andrea Hospital, SAH) in Rome, Italy and a 900-bed hospital (Konkuk University Hospital, KUH) in Seoul, Korea. During the period from March 2012 to July 2013, a total of 340 patients (109 patients from SAH and 231 patients from KUH) were enrolled from the emergency department (n = 224) or intensive care unit (n = 116). They were critically ill patients with suspected sepsis, based on clinical diagnostic criteria of sepsis (e.g. SIRS) [17]. Their medical records were reviewed for the clinical and laboratory data. The protocol was designed following the criteria of the Declaration of Helsinki and was approved by the ethical committee of each participating hospital. The study protocol was approved by the Institutional Review Board (IRB) in each hospital (KUH and SAH). In KUH, written informed consent from the enrolled patients was exempted, because the biomarkers were measured using residual samples that would be discarded, without additional blood sampling from the patients. In SAH, written informed consent was obtained from all enrolled patients for the initial and follow-up data. The patients were divided into five groups (0 – 4) according to the cardiovascular, respiratory, and renal subscores of SOFA score [5]. Their median age was 67.5 years (range, 0 - 102 years), and 177 (52.1%) patients were males. The median duration of hospital stay was 10 days (range, 1 - 838 days), and in-hospital mortality was observed in 51 (15%) patients. Review of the medical history revealed cardiac diseases in 179 (52.6%) patients; diabetes in 90 (26.5%) patients; pulmonary diseases in 78 (22.9%) patients; cancers in 63 (18.5%) patients; gastric diseases in 46 (13.5%) patients; neurologic diseases in 45 (13.2%) patients; and chronic kidney diseases in 36 (10.6%) patients.

Measurement of BNP, NGAL, and PCT
In the whole population, plasma BNP and NGAL were measured using the Triage CarioRenal Panel (Alere, Inc., San Diego, CA, USA), according to the manufacturer’s instruction [18]. It is a fluorescence immunoassay for the quantitative determination of BNP and NGAL in EDTA-anticoagulated whole blood and plasma specimens. Briefly, several drops of EDTA-anticoagulated whole blood are added to the sample port on the device within two hours after blood collection. Then, the blood cells are separated from the plasma using a filter contained in the device. The specimen reacts with fluorescent antibody conjugates and flows through the device by capillary action.

| PCT (ng/mL) | Interpretation | n  | Blood culture positive (%) | Age (yr) | Male (%) |
|------------|----------------|----|---------------------------|----------|----------|
| I (<0.05)  | Healthy        | 28 | 1 (3.6)                   | 68 (5 - 89) | 13 (46.4) |
| II (0.05 – 0.49) | Local infection | 162 | 10 (6.2)                  | 67 (0 - 100) | 90 (55.2) |
| III (0.5 – 1.99) | Systemic infection or sepsis | 75 | 9 (12.0)                  | 655 (0 - 96) | 31 (41.9) |
| IV (2.0 – 9.99) | Severe sepsis  | 42 | 9 (21.4)                  | 70 (0 - 95)  | 20 (47.6) |
| V (≥10)    | Septic shock   | 33 | 11 (33.3)                 | 70 (46 - 102) | 23 (69.7) |
| Total      |                | 340| 40 (11.8)                 | 67.5 (0 - 102) | 177 (52.1) |

Age is expressed as median value (range).
Blood culture-positive rates tended to increase according to the PCT groups, showing significant differences (I vs. V, P = 0.0097; II vs. IV, P = 0.0065; II vs. V, P < 0.0001; III vs. V, P = 0.0184).
PCT: procalcitonin.
The critically ill patients with suspected sepsis were diagnosed based on clinical diagnostic criteria of sepsis (e.g. SIRS) [17].

The critically ill patients with suspected sepsis were diagnosed on the basis of the previous studies and manufacturers' recommendation. PCT concentrations were divided into five groups: < 0.05 ng/mL, group I (healthy); 0.05 – 0.49 ng/mL, group II (local infection); 0.5 – 1.99 ng/mL, group III (systemic infection or sepsis); 2.0 – 9.99 ng/mL, group IV (severe sepsis); and ≥ 10 ng/mL, group V (septic shock) [16,19]. Table 1 shows the distribution of study population according to the PCT concentrations.

Table 1 Comparison of NGAL, creatinine, and BNP according to the sepsis diagnosis

| BNP (pg/mL) | Non-sepsis (n = 221) | Sepsis (n = 119) | PCT-based sepsis (n = 150) |
|-------------|----------------------|-----------------|--------------------------|
|             |                      |                 |                          |
| Clinical sepsis |                      |                 |                          |
| Non-sepsis (n = 221) | 72.3 (52.8 – 115.7) | 140 (65.5 – 189.3) | 66.7 (30.8 – 96.0)        |
| Sepsis (n = 119) | 96.0 (68.0 – 146.5)  | 223.4 (183.6 – 265.0) | 146.5 (93.5 – 223.4)     |
| Creatinine (mg/dL) | 0.94 (0.85 – 1.09)  | 0.84 (0.71 – 1.10) | 0.81 (0.76 – 0.93)       |

| Clinical sepsis | Non-sepsis (n = 221) | Sepsis (n = 119) | PCT-based sepsis (n = 150) |
|-----------------|----------------------|-----------------|--------------------------|
| Non-sepsis (n = 221) | 44.1% (150/340) | 55.9% (190/340) | 44.1% (150/340) |

Table 2 Comparison between clinical sepsis and procalcitonin-based sepsis

| Clinical sepsis | PCT-based sepsis | Kappa (95% CI) |
|-----------------|------------------|----------------|
|                 | Negative (n = 190) | Positive (n = 150) |
| Clinical sepsis |                  |                 |
| Non-sepsis (n = 221) | 144 | 77 | 0.2425 (0.1398 – 0.3453) |
| Sepsis (n = 119) | 46 | 73 | |

Table 3 Comparison of NGAL, creatinine, and BNP according to the sepsis diagnosis

| Clinical sepsis | Non-sepsis (n = 221) | Sepsis (n = 119) | PCT-based sepsis (n = 150) |
|-----------------|----------------------|-----------------|--------------------------|
| BNP (pg/mL)     |                      |                 |                          |
| Non-sepsis (n = 221) | 72.3 (52.8 – 115.7) | 140 (65.5 – 189.3) | 66.7 (30.8 – 96.0) | 146.5 (93.5 – 223.4) |
| Sepsis (n = 119) | 96.0 (68.0 – 146.5)  | 223.4 (183.6 – 265.0) | 146.5 (93.5 – 223.4) |
| Creatinine (mg/dL) | 0.94 (0.85 – 1.09)  | 0.84 (0.71 – 1.10) | 0.81 (0.76 – 0.93) |

P = 0.0001 vs. non-sepsis.

P = 0.0001 vs. non-sepsis.

Data are expressed as median (95% confidence interval).

BNP: B-type natriuretic peptide; NGAL: neutrophil gelatinase-associated lipocalin; PCT: procalcitonin.
Figure 1 (See legend on next page.)
concentrations, these two biomarkers significantly differed between the two groups of PCT-based sepsis. Such a difference was also observed in the comparison of creatinine. For the clinical diagnosis of sepsis, the area under the ROC curve (AUC with 95% CI) for PCT (0.673 [0.621 – 0.723]) differed significantly from those of BNP (0.526 [0.472 – 0.580], \(P = 0.001\)) and NGAL (0.509 [0.455 – 0.564], \(P = 0.005\)). For the PCT-based diagnosis of sepsis, both BNP and NGAL showed an ability to distinguish between the two groups of sepsis. The AUCs (95% CI) for BNP and NGAL were 0.634 (0.580 – 0.685) and 0.594 (0.539 – 0.646), respectively, showing no statistical difference between the two AUCs (\(P = 0.426\)).

The initial and follow-up concentrations of NGAL and PCT were further compared according to the in-hospital mortality (Table 5). In the survivors, the follow-up NGAL and PCT concentrations were significantly lower than their initial concentrations (\(P < 0.0001\) and \(P = 0.0012\), respectively). In logistic regression, they contributed significantly to the prediction of in-hospital mortality. Odds ratios (95% CI) were 1.0032 (1.0012 – 1.0052) and 1.8485 (1.2742 – 2.6815) in NGAL and PCT, respectively.

Discussion

The potential clinical usefulness of some innovative biomarkers has been discussed in the diagnosis, staging, and monitoring of sepsis, and these biomarker-guided strategies may allow more refined risk stratification and lead to improved patient care and outcomes [20,21]. To the best of our knowledge, however, there have been no studies that investigated the three biomarkers of BNP, NGAL, and PCT together in the septic patients so far.

In the present study, we investigated the diagnostic and prognostic utilities of BNP, NGAL, and PCT in critically ill patients with suspected sepsis. In particular, we diagnosed and graded the sepsis based on the PCT concentrations, in addition to the clinical diagnosis. Noticeably, there was a poor agreement between the clinical diagnosis and PCT-based diagnosis of sepsis (Table 2). In spite of this poor agreement, the positive rate of blood culture in the patients with clinical sepsis did not differ from that in the patients with PCT-based sepsis (21.0% vs. 19.3%), and the blood culture-positive rates increased significantly according to the PCT groups (Table 1). Eleven out of 40 patients with positive blood culture belonged to PCT groups I or II. Despite being considered the gold standard for diagnosis, blood cultures are subject to contamination by skin flora if blood cultures are not collected using an appropriate aseptic technique [22]. In this regard, it is possible that the positive blood culture results might have been due to contamination. In recent studies, initial PCT concentrations in the emergency department accurately predicted blood culture positivity in patients with community-acquired pneumonia [23], and PCT showed excellent correlation with bacterial load and

Figure 1 Comparison of BNP, NGAL, and creatinine according to the PCT groups. (A) The BNP concentrations according to the PCT groups were: 109 (5 – 1,220) pg/mL; 42.2 (9 – 2,790) pg/mL; 103.3 (5 – 5,000) pg/mL; 129 (5 – 5,000) pg/mL; and 241 (5 – 1,850) pg/mL, respectively (\(P = 0.0001\)). The median values of BNP were all above the medical decision point (100 pg/mL) in septic patients. (B) The NGAL concentrations according to the PCT groups were: 90.5 (16 – 444) ng/mL; 156 (19 – 1,300) ng/mL; 252 (33 – 1,301) ng/mL; 499.5 (55 – 1,301) ng/mL; and 609 (72 – 1,300) ng/mL, respectively (\(P < 0.0001\)). The median values of NGAL were all above the medical decision point (150 ng/mL) in septic patients. (C) The creatinine concentrations according to the PCT groups were: 0.8 (0.39 – 11.98) mg/dL; 0.82 (0.2 – 9.52) mg/dL; 0.875 (0.2 – 6.9) mg/dL; 1.49 (0.33 – 6.52) mg/dL; and 1.85 (0.4 – 10.61) mg/dL, respectively (\(P < 0.0001\)). The median value of creatinine was above the medical decision point (1.2 mg/dL) only in severe sepsis & septic shock patients.
Table 4 Comparison of BNP, NGAL, and PCT according to the in-hospital mortality

|                          | Total (n = 340) | Clinical sepsis (n = 119) | PCT-based sepsis (n = 150) |
|--------------------------|----------------|--------------------------|---------------------------|
|                          | Survivors (n = 288) | Non-survivors (n = 51) | Survivors (n = 82) | Non-survivors (n = 37) | Survivors (n = 117) | Non-survivors (n = 33) |
| BNP (pg/mL)              |                |                          |                           |                        |                        |                           |
| Survivors                | 69 (46.7 – 101.0) | 200* (159.1 – 280.2)    | 48.2 (13.4 – 143.1)      | 237.0† (165.2 – 356.7) | 112.0 (63.8 – 157.5)  | 253.0† (181.2 – 519.2)  |
| Non-survivors            | 184 (159.1 – 222.7) | 227 (161.4 – 444.9)      | 189 (108.6 – 304.7)      | 218 (143.5 – 375.1)   | 346 (281.9 – 490.6)   | 254 (145.5 – 519.5)     |
| NGAL (ng/mL)             |                |                          |                           |                        |                        |                           |
| Survivors                | 0.27 (0.23 – 0.39) | 0.93‡ (0.54 – 1.35)      | 0.76 (0.43 – 1.52)       | 0.93 (0.63 – 1.34)    |                        |                           |
| Non-survivors            | 0.27 (0.23 – 0.39) | 0.93‡ (0.54 – 1.35)      | 0.76 (0.43 – 1.52)       | 0.93 (0.63 – 1.34)    |                        |                           |
| PCT (ng/mL)              |                |                          |                           |                        |                        |                           |
| Survivors                | 0.27 (0.23 – 0.39) | 0.93‡ (0.54 – 1.35)      | 0.76 (0.43 – 1.52)       | 0.93 (0.63 – 1.34)    |                        |                           |
| Non-survivors            | 0.27 (0.23 – 0.39) | 0.93‡ (0.54 – 1.35)      | 0.76 (0.43 – 1.52)       | 0.93 (0.63 – 1.34)    |                        |                           |

*P = 0.0002 vs. survivors.
†P = 0.0013 vs. survivors.
‡P = 0.0054 vs. survivors.

Data are expressed as median (95% confidence interval).

BNP: B-type natriuretic peptide; NGAL: neutrophil gelatinase-associated lipocalin; PCT: procalcitonin; NA: not applicable.
could discriminate between blood culture contaminants and organisms representing bacteremia [24].

Similar to our data, a multicenter study reported a large disconnect between the perceived severity of heart failure (as assessed by initial disposition and New York Heart Association functional class) and the BNP level, emphasizing the biomarker-guided therapeutic and monitoring strategies involving BNP in the patients with heart failure [9]. Another interesting finding is that the BNP and NGAL concentrations demonstrated significant differences according to the presence or absence of sepsis only when they were compared according to the PCT-based sepsis (Table 3). Based on these results, PCT-based sepsis diagnosis seems to be more reliable and discriminating than clinical sepsis diagnosis.

The assessment of risk stratification and prognosis in sepsis is based on the clinical scoring systems. However, they are in general inefficient to provide definite clues on organ dysfunctions or failures [5,20]. In this study, BNP, NGAL, and creatinine all showed significant differences according to the PCT groups (Figure 1). Although creatinine was increased only in the patients with severe sepsis & septic shock, BNP and NGAL were increased above their medical decision points in all septic patients. Compared with creatinine, NGAL seems to be an early, objective marker of AKI in relation to sepsis [16]. Moreover, the BNP concentration was significantly associated with the cardiovascular and renal subscres of SOFA score, and the NGAL concentration was significantly associated with the renal subscore of SOFA score (Figure 2). Taken together, these findings imply the clinical usefulness of these innovative biomarkers to assess the organ dysfunctions or failures along with the sepsis severity.

We also observed the significant differences of these biomarkers according to the in-hospital mortality (Table 4). The initial BNP and PCT concentrations were significantly higher in the non-survivors than in the survivors, and both BNP & PCT showed an equal ability to predict in-hospital mortality. In the survivors, the follow-up NGAL and PCT concentrations were significantly lower than their initial concentrations (Table 5). The present findings support the previous studies, which showed the usefulness of these biomarkers for prognostic stratification in various critical care settings [15,25,26]. PCT seems to be associated with the diagnosis and severity of sepsis, BNP with response to circulatory and cardiovascular complications, and NGAL with AKI in severe sepsis/septic shock. Compared with PCT and BNP, NGAL did not seem to correlate with mortality. This study is partly limited in that the follow-up data of biomarkers were available only in one third of the enrolled patients and included only NGAL and PCT. Accordingly, it is difficult to draw any conclusions from these results, and serial measurement of these biomarkers would be valuable to estimate the adverse outcomes in the patients with sepsis.

**Table 5 Comparison of NGAL and PCT at initial and follow-up measurements according to the in-hospital mortality**

|                      | Survivors (n = 96) | Non survivors (n = 13) |
|----------------------|-------------------|-----------------------|
|                      | Initial measurement (mean ± SD) | Follow-up measurement (mean ± SD) | Initial measurement (mean ± SD) | Follow-up measurement (mean ± SD) |
| NGAL (ng/mL)         | 214.5 ± 249.1      | 148.7 ± 173.3         | 727.4 ± 554.5                  | 775.7 ± 562.1                  |
| PCT (ng/mL)          | 5.56 ± 15.4        | 0.61 ± 2.18†          | 31.8 ± 72.6                    | 18.4 ± 37.4                    |

*P < 0.0001 vs. initial measurement.

†P = 0.0012 vs. initial measurement.

Both initial and follow-up data were available in 109 patients (96 survivors and 13 non-survivors).

NGAL: neutrophil gelatinase-associated lipocalin; PCT: procalcitonin; SD: standard deviation.
Procalcitonin and sepsis: recent data on

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