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Is plasma neutrophil gelatinase-associated lipocalin a predictive biomarker for acute kidney injury in sepsis patients? A systematic review and meta-analysis☆

Sollip Kim, MD [a,1], Hyun-Jung Kim, MD [b,1], Hyeong-Sik Ahn, MD [b], Ji Yang Song, RN [b], Tae-Hyun Um, MD [a], Chong-Rae Cho, MD [a], Hoon Jung, MD [c], Hyeon-Kyoung Koo, MD [c], Joo Hyun Park, MD [c], Sung-Soon Lee, MD [c], Hye Kyeong Park, MD [c,*]

[a] Department of Laboratory Medicine, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Gyeonggi, Korea
[b] Department of Preventive Medicine, Korea University Medical College, Seoul, Korea
[c] Department of Internal Medicine, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Gyeonggi, Korea

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ABSTRACT

Purpose: Neutrophil gelatinase-associated lipocalin (NGAL) is a useful biomarker for early diagnosis of acute kidney injury (AKI). However, the diagnostic value of NGAL for predicting AKI in sepsis patients is unclear.
Methods: MEDLINE, EMBASE, and Cochrane Library databases were searched to identify research publications.
Results: Twelve studies from 9 countries including a total of 1582 patients, of whom 315 (19.9%) developed AKI, were included in the study; plasma NGAL levels were significantly higher in adult sepsis patients with AKI than in those without AKI (mean difference, 274.65; 95% confidence interval [CI], 106.16-443.15; $I^2 = 94\%$). Urine NGAL levels were not significantly different. The diagnostic odds ratio of plasma NGAL for predicting AKI in sepsis patients was 6.64 (95% CI, 3.80-11.58). The diagnostic accuracy of plasma NGAL was 0.881 (95% CI, 0.819-0.923) for sensitivity, 0.474 (95% CI, 0.367-0.582) for specificity, 0.216 (95% CI, 0.177-0.261) for positive predictive value and 0.965 (95% CI, 0.945-0.977) for negative predictive value.
Conclusion: Plasma NGAL has a high sensitivity and a high negative predictive value for detection of AKI in adult sepsis patients. However, its low specificity and low positive predictive value could limit its clinical utility. The usefulness of urine NGAL was not revealed in this study.

1. Introduction

Even when physicians start to treat an infection early, sepsis can develop and progress to severe sepsis or septic shock [1]. Moreover, severe sepsis or septic shock can both lead to multiorgan dysfunction syndrome, which includes acute kidney injury (AKI) in critically ill patients [2–4]. During sepsis, cytokines such as tumor necrosis factor–α, interleukin-6, and interleukin-10 launch various signal cascades that can lead to the development of AKI [5,6]. Because organ dysfunction syndrome in critically ill patients is associated with substantial morbidity and mortality [3], early diagnosis and treatment of AKI can improve sepsis prognosis and decrease the number of cases requiring renal replacement therapy [7,8].

The diagnosis of AKI is generally based on increased serum creatinine levels and the presence of oliguria. According to the Acute Kidney Injury Network (AKIN) criteria, *AKI* is defined as an abrupt (within 48 hours) reduction in kidney function, showing an absolute increase in serum creatinine of at least 0.3 mg/dL (≥26.4 μmol/L) or a relative increase in serum creatinine of at least 50% (1.5-fold from baseline) [9]. The AKIN criteria are a modified version of the Risk, Injury, Failure and Loss, End-Stage Renal Disease (RIFLE) criteria that use changes in serum creatinine levels, glomerular filtration rate, and/or urine output [10] and remain in use for diagnosis of AKI. However, serum creatinine may slowly increase over several days of kidney insults [11], and severe AKI can occur in patients with a normal urine output. In addition, performing hourly measurements of urine output is difficult, and diuretics and hemodynamic status affect urine volume [12].

The novel biomarker neutrophil gelatinase-associated lipocalin (NGAL) has recently been studied as a promising, highly sensitive, and specific early marker of AKI [13,14]. NGAL, also known as *lipocalin-2*, is a 178–amino acid polypeptide expressed by neutrophils and epithelial

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* Corresponding author at: Department of Internal Medicine, Ilsan Paik Hospital, Inje University College of Medicine, Joowha-ro 170, Ilsanseo-gu, Goyang, Gyeonggi, 411-706, Republic of Korea. Tel.: +82 31 910 7544; fax: +82 31 910 7219.
E-mail address: stella_park@paik.ac.kr (H.K. Park).

[1] Sollip Kim and Hyun-Jung Kim contributed equally to this work.

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cells, including proximal tubule epithelial cells in normal kidney, lung, stomach, and colon tissues [15]. Its expression increases in the kidney after ischemic or nephrotoxic injury [16,17]. In kidney tubules, the messenger ribonucleic acid for NGAL is upregulated within a few hours after various harmful stimuli [18]. Impaired proximal tubular reabsorption in the setting of proximal tubular injury may further potentiate increased urinary NGAL levels [17,19–21]. Circulating NGAL is synthesized in the bone marrow and stored in neutrophils [22]. Neutrophils, a critical component of the innate immunity to bacterial infection, release the contents of their granules in response to bacterial infections and nonspecific inflammatory stimuli [23–25]. Plasma NGAL increases noticeably with a reduction in glomerular filtration rate in stable chronic kidney disease patients, potentially producing a very high number of false-positive diagnoses for AKI in a study with nonseptic patients [26]. However, the results of recent studies have been inconsistent regarding the diagnostic value of plasma and urine NGAL levels in patients with sepsis and AKI [27–29]. The systematic review by Hjortrup et al [30] did not report results of subgroup analyses of measurements of plasma and urine NGAL levels in patients with sepsis and AKI because of study heterogeneity and lack of data. Therefore, we performed a systematic review and meta-analysis to evaluate the diagnostic value of plasma and urine NGAL levels as early biomarkers of AKI in patients with sepsis.

2. Materials and methods

We used comprehensive databases to search for studies evaluating the diagnostic value of plasma and urine NGAL. This study was based on the Cochrane methods for Systematic Reviews of Diagnostic Test Accuracy [31] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [32].

2.1. Data and literature sources

We searched the following databases: PubMed-MEDLINE (January 1, 1976, to July 16, 2014), EMBASE (January 1, 1985, to July 16, 2014), Cochrane Library (January 1, 1987, to July 16, 2014), and KoreaMed (June 1, 1958, to July 16, 2014). Electronic database searches used the following keywords and Medical Subject Headings terms: *(Sepsis OR Septicemia OR Septic) AND (Lipocalin OR LCN2 protein OR NGAL)* (see Supplement 1 for details of the search strategies). The search strategies were based on Medical Subject Headings terms combined with free-text terms and modified for other databases. After the initial electronic search, we manually searched the bibliographies from identified studies. Duplicate records identified by authors, title, and journal citation were excluded. We did not use any other restrictions in our searches.

2.2. Study selection

All studies were required to meet the following inclusion criteria: (1) including patients of all ages admitted to the emergency department (ED) or intensive care unit (ICU) with a diagnosis of sepsis, (2) including comparison between septic AKI and septic non-AKI groups, and (3) reporting measurements of plasma or urine NGAL for each group. Prospective and/or retrospective studies were included. Studies that did not compare NGAL levels between septic AKI and septic non-AKI groups were excluded. Also, studies that had a different aim (eg, NGAL as a marker for predicting sepsis) were excluded (Fig. 1).

Sepsis was defined as a suspected or proven infection, with evidence of 2 or more systemic inflammatory response syndrome (SIRS) criteria according to the definitions of the American College of Chest Physicians/Society of Critical Care Medicine consensus criteria [1]. Patients with sepsis-induced tissue hypoperfusion or organ dysfunction were classified as suffering severe sepsis. *Septic shock* was defined as severe sepsis with hypotension, despite adequate fluid resuscitation. AKI was defined using the RIFLE/AKIN criteria for adults. For children, the authors adopted various AKI criteria, including a modified RIFLE/AKIN and Kidney Disease; Improving Global Outcomes (KDIGO) AKI staging. The criteria used to define sepsis and AKI by each study are presented in Supplement 3.

Two authors (S Kim and HK Park) independently screened the titles and abstracts of identified studies from electronic searches and then obtained the full text of potentially appropriate studies for evaluation. Any difference in the authors' selection of studies was resolved by discussion.

2.3. Data extraction

Using the predefined data extraction form, the 2 authors (S Kim and HK Park) blindly extracted data from the included studies. The following variables were extracted: (1) mean and SD (or median and interquartile range) of plasma and urine NGAL in the AKI and non-AKI groups; (2) sensitivity and specificity of plasma NGAL tests for prediction of AKI in sepsis patients; (3) demographics (eg, age, sex, number of patients in the AKI and non-AKI groups), (4) AKI diagnostic criteria and sepsis diagnostic criteria; (5) specimen type; and (6) method of NGAL assessment. If data were missing or additional information was required, the author of original paper was contacted via email.

2.4. Assessment of methodological quality

The methodological quality of included studies was independently assessed by 2 authors (S Kim and HK Park) using the Quality Assessment of Diagnostic Accuracy Studies–2 tool [33]. We used the standard signaling questions from the Quality Assessment of Diagnostic Accuracy Studies–2 tool and decided that the risk of bias for each domain was high if the answer to at least one signaling question for each domain was "no." If the measurement of NGAL was performed within 24 hours after admission, the risk of index test bias was considered to be low. Any discrepancy between authors was resolved through discussion or through review by the third author (HJ Kim). Judgments of risk of bias and applicability are presented in Supplement 2.

2.5. Statistical analysis

The primary outcomes of this study were plasma and urine NGAL levels of sepsis patients in the AKI and non-AKI groups. We calculated the mean difference in plasma and urine NGAL levels via the inverse variance method using the mean and SD from each study. Subgroup analysis was performed based on age and biomarker measurements.

We conducted sensitivity analyses for situations where this might affect the results (sex, storage method, sepsis severity, illness severity, underlying disease, study design, study population [ED and ICU], risk of bias). We divided all selected studies for sensitivity analysis into 2 groups (only septic shock patients study and others) according to the sepsis severity. Majority of the studies presented the Sepsis-related Organ Failure Assessment (SOFA) score as an illness severity, so we divided the studies according to the SOFA score greater than 11 as a cutoff value [34].

The secondary outcome was the diagnostic value of plasma and urinary NGAL for AKI in sepsis patients. We used the Stata command metandi [35], which fit the hierarchical logistic regression models and calculated the sensitivity, specificity, positive and negative likelihood ratios, and the diagnostic odds ratio (DOR) using the true positives, false positives, false negatives, and true negatives within each study. In this review, we calculated the positive predictive value (PPV) using the positive likelihood ratio and the negative predictive value (NPV) using the negative likelihood at the median prevalence [36]. For each index test, estimates of the diagnostic accuracy were expressed as sensitivity and specificity, displayed as coupled forest plots, and plotted in a hierarchical summary receiver operating characteristic space. All values were calculated with 95% confidence intervals (CIs). A bivariate normal model was used to analyze differences in sensitivity and specificity