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Original Article

Predictive value of plasma neutrophil gelatinase-associated lipocalin for acute renal failure in patients with severe sepsis

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Abstract

Background: Predicting acute renal failure in patients with severe sepsis is important, because patients may need renal replacement therapy (RRT). Neutrophil gelatinase-associated lipocalin (NGAL) has been evaluated for its ability to detect and predict acute kidney injury (AKI) in critically ill patients. This study aimed to assess the predictive value of plasma NGAL for acute renal failure in adult severely septic patients.
Methods: Thirty healthy adults and 85 adult patients admitted to the medical intensive care unit (ICU) were enrolled. Serum creatinine, plasma NGAL, and interleukin (IL)-6, IL-10, and IL-17 levels were evaluated. AKI was classified as Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE).
Results: RIFLE-Failure (RIFLE-F) developed in 30 of 76 (39.5%) patients with severe sepsis without chronic kidney disease within 7 days after ICU admission. Serum creatinine, plasma NGAL, IL-6, and IL-10 could predict RIFLE-F within 7 days after ICU admission. The discriminatory power of plasma NGAL was not significant for predicting hospital mortality. The area under the receiver operating characteristic curve of plasma NGAL was not higher than that of serum creatinine in predicting RIFLE-F within 7 days.
Conclusion: Plasma NGAL is a useful tool for predicting acute renal failure in adult patients with severe sepsis. Serum creatinine has a similar ability to detect RIFLE-F occurrence.

Keywords: acute kidney injury; biomarkers; neutrophil gelatinase-associated lipocalin; renal replacement therapy; severe sepsis

1. Introduction

Sepsis is a leading cause of acute kidney injury (AKI) in critically ill patients.[1,2] AKI is an important issue that increases mortality among patients with severe sepsis.[3] In current clinical practice, the proportional change of serum creatinine is the most common indicator of renal dysfunction. However, its slow rate of change has limited its application for diagnosing and predicting AKI.[4–6] Recently, several studies have investigated the early detection and prediction of AKI by neutrophil gelatinase-associated lipocalin (NGAL) as a novel biomarker,[4,6–11] although NGAL from activated neutrophils is also a marker of infection and systemic inflammation.[12–14] When severe sepsis is complicated by AKI, the predictive performance of NGAL may be affected.

Sepsis is a complicated syndrome in which proinflammatory cytokines like interleukin (IL)-6 and anti-inflammatory cytokines like IL-10 are expressed simultaneously.[15] Previous studies have shown that elevated levels of

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such cytokines predict AKI development and mortality in patients with sepsis and AKI.[16–18] IL-17 is reported to play a role in the pathogenesis of AKI.[19] Can IL-6, IL-10, and IL-17 also be useful markers for acute renal failure in patients with severe sepsis?

The optimal timing for initiating renal replacement therapy (RRT) for AKI in patients with severe sepsis has not been established. The Acute Dialysis Quality Initiative (ADQI) proposed a consensus definition for the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification for AKI, grading severity by risk, injury, and failure.[20] Two studies suggested that early RRT prior to RIFLE-Failure (F) stage may improve the outcome of AKI patients who need RRT.[21,22] Promising AKI biomarkers to predict RIFLE-F may allow for the optimal timing of initiating RRT.

The main purpose of this study was to evaluate the potential for plasma NGAL and cytokines to predict RIFLE-F and RRT initiation in patients with severe sepsis.

2. Methods

2.1. Participants

This was a prospective observational study of 115 patients who had undergone tests for plasma neutrophil gelatinase-associated lipocalin (NGAL) and cytokines. Seventy-six adult patients did not have a history of chronic kidney disease (CKD) or end-stage renal disease. CKD was defined as decreased kidney function (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) for ≥ 3 months.[23] Nine patients had end-stage renal disease (RIFLE-E) and received regular hemodialysis. These 85 patients were admitted to the medical intensive care unit (ICU) at Chang Gung Memorial Hospital in Keelung, Taiwan due to severe sepsis from July 2008 to August 2010. Thirty healthy adults were recruited from the hospital's health evaluation center (Fig. 1). The ICU was a closed-format unit staffed by medical intensivists. The hospital's Institutional Review Board approved the study (99-2232B), and the patients' families provided informed consent.

2.2. Clinical data collection and definitions

Within the first 24 hours of admission, data on patients' age, gender, medical history, infection source, and comorbidity were recorded. Standard treatment, including fluid resuscitation, broad-spectrum antibiotics, drainage, and basic support were provided to all patients.[24] Antibiotics and fluid resuscitation were started as soon as possible after sepsis was diagnosed.

Severe sepsis and septic shock were defined according to the criteria of the Consensus Conference.[25] Systemic inflammatory response syndrome (SIRS) was defined as two or more of the following criteria: (1) body temperature $> 38°C$ or $< 36°C$; (2) respiratory rate > 24 breaths/min; (3) heart rate > 90 beats/min; and (4) white blood count $> 12{,}000/\mu L$ or $< 4000/\mu L$ or $> 10\%$ bands. Sepsis was defined as SIRS based on confirmed or suspected microbial etiology, while severe sepsis was defined as sepsis with one or more of organ dysfunction or with hypotension. Septic shock was defined as sepsis with hypotension unresponsive to fluid resuscitation and further requiring vasopressors to maintain blood pressure on admission day. Survivors were defined as patients who were still alive 28 days after ICU admission. Disease severity was assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II score using data within 24 hours of admission.[26]

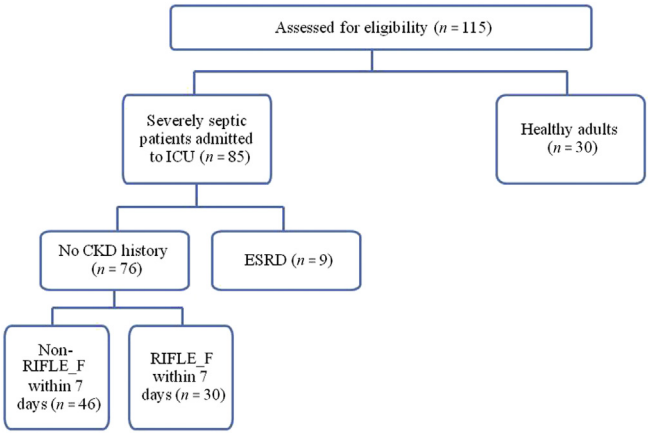

Fig. 1. The study profile shows 115 individuals including 30 healthy adults and 85 patients with severe sepsis admitted to the ICU. Nine patients had ESRD and received regular hemodialysis. Seventy-six adult patients did not have a history of CKD or ESRD. In the 76 patients with severe sepsis, 30 patients had RIFLE-F within 7 days after ICU admission and 46 patients did not. CKD = chronic kidney disease; ESRD = end-stage renal disease; ICU = intensive care unit; RIFLE-F = Failure stage of Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease classification.

AKI was defined using serum creatinine and urine output criteria to determine the RIFLE classification of all patients. The criteria that led to the worst possible classification were used. Because some patients ($n = 8$, 10.5%) did not have baseline renal function, a hypothetical baseline serum creatinine was estimated for a given patient assuming a normal glomerular filtration rate (75 mL/min per 1.73 m^2) with modification of diet in renal disease (MDRD) formula, as recommended by the ADQI working group.[20,23]

2.3. NGAL and cytokine measurements

Plasma samples were obtained from veins within 24 hours after admission to the medical ICU. All plasma samples were stored at $-80°C$ until centrifugation within 2 hours. Plasma levels of IL-6, IL-17, and NGAL were measured by human IL-6, IL-17, and NGAL enzyme-linked immunosorbent assay (ELISA) kits (R & D Systems, Minneapolis, MN, USA). Plasma level of IL-10 was measured by human IL-10 ELISA kit (Pierce Biotechnology, Rockford, IL, USA).

2.4. Statistical analysis

Statistical analysis was performed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). Differences in