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The value of serial serum cell adhesion molecules in predicting acute kidney injury after severe sepsis in adults

Chih-Min Su [a,b], Hsien-Hung Cheng [b], Chih-Wei Hung [b], Sheng-Yuan Hsiao [a,b], Nai-Wen Tsai [c], Wen-Neng Chang [c], Hung-Chen Wang [d], Wei-Che Lin [e], Ben-Chung Cheng [a,f], Yu-Jih Su [f], Ya-Ting Chang [a,c], Chia-Te Kung [b,1], Cheng-Hsien Lu [a,c,g,*,1]

[a] Department of Biological Science, National Sun Yat-Sen University, Kaohsiung, Taiwan, ROC
[b] Department of Emergency Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, ROC
[c] Department of Emergency Neurology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, ROC
[d] Department of Emergency Neurosurgery, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, ROC
[e] Department of Emergency Radiology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, ROC
[f] Department of Emergency Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, ROC
[g] Department of Neurology, Xiamen Chang Gung Memorial Hospital, Xiamen, Fujian, PR China

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ABSTRACT

Background: Septic acute kidney injury (AKI) is a common complication of severe sepsis. We tested the hypothesis that serum cell adhesion molecule levels are substantially increased in early septic AKI and decreased after antimicrobial therapy and their level can predict prognosis.
Methods: Seventy-two nontraumatic, nonsurgical adult patients with severe sepsis admitted to the emergency department were evaluated. Serum adhesion molecules were collected and assessed. We evaluated their relationship with early septic AKI compared with other clinical predictors and biomarkers.
Results: Forty-five patients (62.5%) experienced early septic AKI. Patients with septic AKI also were more likely to experience septic shock and respiratory failure and had higher in-hospital mortality. Stepwise logistic regression model revealed that E-selectin level, septic shock, and respiratory failure were independently associated with septic AKI and each 1 ng/ml increase in serum E-selectin level increased the risk of septic AKI by 1%. Furthermore, the E-selectin levels in the septic AKI group were significantly higher than those in the non-AKI group at two different times (days 1 and 4).
Conclusion: WE show that early septic AKI implies a higher mortality in severe sepsis patients and that E-selectin level at presentation is a powerful predictor of early septic AKI.

1. Introduction

Septic acute kidney injury (AKI) is a common complication of severe sepsis and septic shock [1]. It is estimated that 50–75% of patients with severe sepsis develop AKI [2–4]. AKI is also an independent clinical predicator for the increased mortality and poor outcome in severe sepsis patients [5]. Several mechanisms have been proposed, including renal ischemia, glomerular and vascular microthrombosis, renal hyperemia, and inflammatory apoptosis [1,6,7].

Fortunately, understanding the early stress response of AKI has revealed a number of proteins that indicate early pathophysiology and, serendipitously, represent potential biomarkers [8–10]. Most previous studies have demonstrated that levels of these biomarkers are also increased during other chronic and acute inflammatory conditions independent of the degree of kidney injury; however, standardized clinical platforms for their measurement are not currently available [10,11].

Endothelial cells play an essential role in the development of inflammatory processes by amplifying the immune response [12]. These are mediated by the augmented expression of adhesion molecules, including intercellular cell adhesion-molecule-1 (ICAM-1), endothelial selectin (E-selectin), platelet selectin (P-selectin), and vascular cell adhesion molecule-1 (VCAM-1), which help circulating leukocytes emigrate into tissues [13]. Our recent studies demonstrated that these are promising biomarkers of organ dysfunction following acute severe sepsis [14,15].

* Corresponding author at: Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, No. 123, Ta Pei Road, Niao Sung Hsiang, Kaohsiung City 833, Taiwan, ROC.
E-mail addresses: chlu99@ms44.url.com.tw, chlu99@adm.cgmh.org.tw (C.-H. Lu).
[1] Drs. Cheng-Hsien Lu and Chia-Te Kung contributed equally to this work.

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Several animal studies have revealed that cell adhesion molecules are essential for neutrophil recruitment into the kidney capillary plexus, which is a hallmark of ischemia-reperfusion kidney injury [16–19].

2. Patients and methods

2.1. Study population

This was a prospective study on the time course of serum adhesion molecule levels in severe sepsis and septic shock patients and the association of these biomarkers with early septic AKI. Patients aged ≥20 years who were consecutively admitted to the emergency department (ED) of Kaohsiung Chang Gung Memorial Hospital (CGMH) were screened daily for severe sepsis and septic shock according to specific criteria and enrolled in the study within 24 h after recognition of meeting the criteria. The hospital's Institutional Review Committee on Human Research approved the study protocol, and all patients provided informed consent.

Severe sepsis on ED admission was defined according to the American College of Chest Physicians/Society of Critical Care Medicine criteria [20]: 1) suspected or confirmed infection, 2) two or more manifestations of systemic inflammatory response syndrome, and 3) at least one sepsis-induced acute organ dysfunction or signs of hypoperfusion. All patients who met these three criteria were included. Septic shock was defined as severe sepsis associated with hypotension not controlled by vascular expansion and required vasopressive agents to maintain systolic blood pressure >100 mmHg. To prevent confounding factors that could also contribute to kidney dysfunction, patients were excluded on the following criteria: traumatic etiology; surgical treatment; underlying hematologic diseases or undergoing chemotherapy; pregnancy; end-stage renal disease and undergoing dialysis; history of exposure to contrast media, angiotensin converting enzyme inhibitor, nonsteroidal anti-inflammatory drug, or any other substance known to cause renal function impairment; transferred from another hospital.

2.2. Clinical assessment and treatment

Demographic data were collected as well as Acute Physiology and Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment (SOFA), and Charlson Comorbidity Index (CCI) scores, which were calculated during the first 24 h of admission to assess the severity of organ dysfunction. Hemodynamic status at triage and shock within 24 h were recorded. Basic laboratory tests were conducted, and lactate concentration and inflammatory markers including plasma C-reactive protein (CRP) and procalcitonin levels were measured on ED admission. Moreover, the course of various organ dysfunctions and supportive treatments such as vasoactive and ventilator therapies and steroid therapies was recorded.

2.3. Definition of septic AKI

Serum creatinine levels of the enrolled patients were checked at least every 3 days in the first 7 days of the event. AKI was determined based on serum creatinine levels. The definition for AKI in our experiment was based on the Kidney Disease: Improving Global Outcomes (KDIGO) criterion of an increase in serum creatinine of 0.3 mg/dl developing over 48 h or ≥50% developing over 7 days [21]. We also estimated the ratio of the highest creatinine level during the first 7 days to the baseline serum creatinine level, to determine whether there was a correlation with inflammatory biomarkers. For patients who could not achieve the baseline serum creatinine level, we used the lowest level of serum creatinine during admission as the baseline level. In this study, the increased serum creatinine ratio was defined as the highest serum creatinine level during the first 7 days divided by the baseline creatinine level, and the ratio of blood urea nitrogen divided by serum creatinine at presentation was considered as a parameter to determine the cause of the AKI.

2.4. Assessment of infection biomarkers

All tests were conducted by the quality-controlled central laboratory of CGMH. Concentrations of CRP were determined by enzyme immunoassay (EMIT; Merck Diagnostics), whereas procalcitonin was measured using an enzyme-linked fluorescent assay (Vidas; bioMerieux). Serum lactate levels were measured using a serum-based assay catalyzed by lactate oxidase (UniCel Integrated System; Beckman Coulter Inc.).

2.5. Blood sampling and assessment of serum adhesion molecules

Blood samples of serum adhesion molecules were collected on the first day of enrollment (day 1). Additional samples were obtained on days 4 and 7. Blood samples were collected using venipuncture into Vacutainer SST tubes. Blood was allowed to clot at room temperature for a minimum of 30 min, and the clot was removed by immediate centrifugation at 3,000 rpm for 10 min at 4°C. All serum samples were collected after centrifugation, isolated, and stored at −80°C in multiple aliquots. Serum soluble ICAM-1 (sICAM-1), sVCAM-1, sE-selectin, sL-selectin, and sP-selectin levels were determined by using a commercially available enzyme-linked immunosorbent assay kit (R&D Systems) in which standards, controls, and unknown samples were incubated in microtitration wells coated with marked antibodies (i.e., anti-ICAM-1, anti-VCAM-1, anti-P-selectin, anti-E-selectin, and anti-L-selectin). After incubation and washing, the wells were treated with another anti-Ag detection antibody labeled with horseradish peroxidase.

After a second incubation and washing, the wells were incubated with the substrate tetramethylbenzidine. An acidic stopping solution was then added, and the enzymatic turnover rate of the substrate was determined by dual-wavelength absorbance measurement at 450 and 620 nm. The absorbance was directly proportional to the concentration of the antigens present. A set of antigen standards was used to plot a standard curve of absorbance versus antigen concentration, from which the antigen concentrations in the unknowns were calculated.

2.6. Statistical analysis

Data are expressed as mean ± standard deviation. Univariate analyses were compared by using Student's *t* test, whereas categorical variables were compared by using the χ^2 test or Fisher's exact test, as appropriate. Correlation analysis was used to explore the relationships between lactate, CRP, procalcitonin, and serum adhesion molecule levels on day 1 with the increased serum creatinine ratio. Repeated measures of ANOVA were used for comparing biomarkers among three intervals (at presentation (day 1), day 4, and day 7). We used Scheffé multiple comparison method to analyze the intraindividual changes in parameters over time and to compare parameters between the different groups (AKI and non-AKI) of severe sepsis patients. Stepwise logistic regression was used to evaluate the relationships between significant variables and AKI, with adjustments for other potential confounding factors. Receiver operating characteristic (ROC) curves were generated to determine a cutoff level for significant variables for AKI. Sensitivity and specificity were assessed as equally significant. The areas under the ROC curves (AUCs) were calculated for each parameter and compared. All statistical analyses were conducted using the SAS software package, version 9.1 (SAS Statistical Institute).

3. Results

3.1. Baseline characteristics of the study patients

Seventy-two adult severe sepsis and septic shock patients were enrolled in this study. These 72 patients included 25 women and 47