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Ischemia-modified albumin is a predictor of short-term mortality in patients with severe sepsis

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ABSTRACT

Purpose: One of the most important events leading to morbidity and mortality in patients with severe sepsis is the development of global tissue hypoperfusion and oxidative damage. Ischemia-modified albumin (IMA), an albumin generated under ischemic and oxidative conditions, is a marker of oxidative stress and hypoperfusion. Here, we investigated whether IMA level could predict short-term mortality with severe sepsis.
Methods: A prospective cohort study was conducted from April 2014 to October 2014 in intensive care units in a tertiary hospital. At the onset of severe sepsis, serum IMA level was measured, and baseline and laboratory data, infection sources, and underlying diseases were recorded; Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation II scores were calculated. Multivariate logistic regression and receiver operating characteristic curve analyses were used to evaluate predictors of mortality. Kaplan-Meier analysis was used to compare survival at day 28.
Results: A total of 117 patients with severe sepsis were included (overall 28-day mortality, 24.8%). The IMA level was higher in nonsurvivors than in survivors ($P < .05$). It was a strong predictor of 28-day mortality (area under the receiver operating characteristic curve, 0.742; $P < .001$), and the optimal cutoff for IMA level maximizing sensitivity and specificity was 110 U/mL. On multivariate logistic regression, Acute Physiology and Chronic Health Evaluation II score and IMA level were independent risk factors for death. Survival rate was reduced with very high IMA level (≥110 U/mL; $P < .05$).
Conclusions: The IMA level, especially at least 110 U/mL, may be a useful predictor of death for patients with severe sepsis.

1. Introduction

Sepsis is the presence or presumed presence of an infection accompanied by evidence of a systemic response called the systemic inflammatory response syndrome [1]. It is a major source of morbidity and mortality throughout the world [2]. Despite advances in the management of sepsis, it is still the second leading cause of death in noncoronary intensive care units (ICUs) [3]. To improve clinical outcomes with sepsis, patients who are at risk for short-term mortality should be identified and the clinical decision-making process optimized [4].

One of the most important events leading to morbidity and mortality in patients with severe sepsis is the development of global tissue hypoperfusion and after oxidative damage [5,6]. Tissue hypoperfusion and hypoxia could lead to mitochondria dysfunction and generalized reactive oxygen species (ROS) production, then further extensive oxidative stress damage to cells and tissues [7]. Sepsis-induced ischemia and oxidative damage conceivably play a key role in the pathogenesis of organ dysfunction and are believed to be the prelude to the development of multiple organ failure and death [8]. Early recognition of the above progress may be helpful for timely clinical intervention.

Ischemia and the generation of ROS can alter the ability of the N-terminal region of the albumin molecule to bind transitional metallic ions such as cobalt, copper, and nickel [9]. This modification of albumin, called ischemia-modified albumin (IMA), can be measured by albumin

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cobalt binding assay [10]. Ischemia-modified albumin was first measured to detect early myocardial ischemia before the onset of myocardial necrosis [11]; since then, increasing evidence showed elevated IMA levels in most patients with ischemic events (eg, cerebrovascular occlusion, pulmonary ischemia, gastrointestinal ischemia, and muscle ischemia) and conditions that are potent producers of free radicals (eg, liver cirrhosis, renal failure, and advanced cancers) [12-17]. Ischemia-modified albumin is a marker of oxidative stress and ischemia reperfusion in different clinical conditions [18,19] and has prognostic value in patients with end-stage renal diseases, acute coronary diseases, or their preoperative status [20-24].

In patients with sepsis, IMA level can be used to quantify the degree of ischemia and oxidative stress [25] and may be a biomarker of outcome and death. However, there is a dearth of data regarding the prognostic value of IMA levels in such patients. Here, we prospectively collected data on patients with severe sepsis admitted to ICUs in a teaching hospital and investigated whether IMA level could predict short-term (28-day) mortality.

2. Methods

2.1. Setting and patients

A prospective observational cohort study was performed from April 2014 to October 2014 in Qilu Hospital of Shandong University, a 3300-bed teaching hospital. The following ICUs were included in this study: mixed (50 beds), surgical (12 beds), and respiratory (12 beds). The study was approved by the ethics committee of Qilu Hospital of Shandong University and performed according to the ethical standards in the Helsinki Declaration of 1975. A waiver for informed consent was granted by the ethics committee considering that this was an observation study without any intervention for patients.

Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection. *Severe sepsis* is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion according to the international guidelines of the Surviving Sepsis Campaign [4]. *Septic shock* is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation (systolic blood pressure <90 mm Hg despite adequate fluid resuscitation, mean arterial blood pressure <70 mm Hg, or a reduction of 40 mm Hg in systolic blood pressure from baseline in the absence of other causes of hypotension) [4].

Inclusion and exclusion of patients are summarized in Fig. 1. Subjects were excluded if they (1) had other ischemic diseases such as acute coronary syndrome, acute ischemic cerebrovascular disease, acute pulmonary embolism, or acute lower-limb arterial or venous embolisms, and aortic dissection; (2) had preexisting malignant arrhythmia or cardiac arrest; (3) had an undrained source of surgical sepsis; (4) were younger than 18 years, with AIDS, or pregnant; (5) had extremely low or high serum albumin levels (<20 or >55 g/L) [26,27]; or (6) died within 24 hours or had a length of stay less than 72 hours, or had do-not-resuscitate orders. All patients received appropriate treatment according to the international guidelines of the Surviving Sepsis Campaign [4]. Within 24 hours after the onset of severe sepsis, data on patient demographics, sources of infection, laboratory results, and comorbidities were collected, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were calculated. Only 1 primary infection source for each patient was recorded. The primary outcome was 28-day mortality.

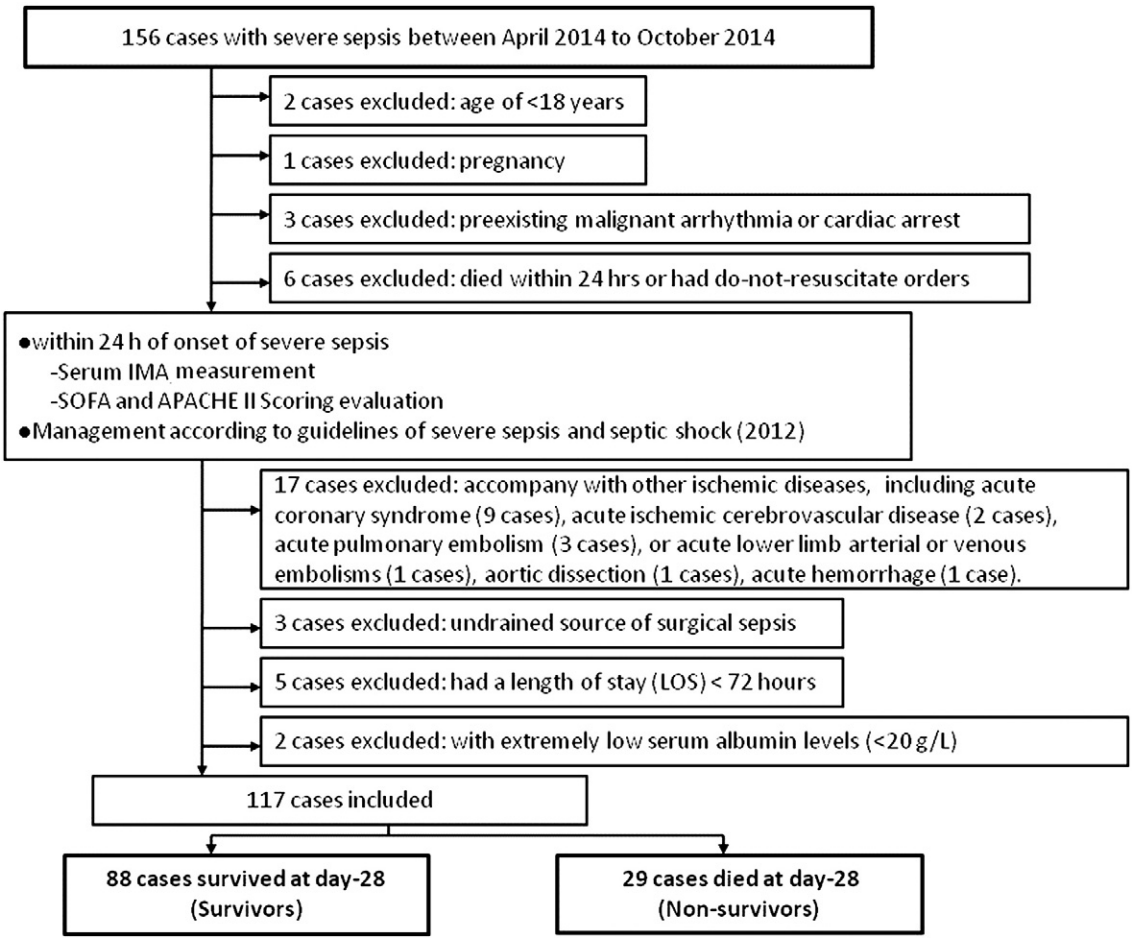

Fig. 1. Flow diagram of inclusions and exclusions for patients with severe sepsis.