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Full Length Article

The role of biomarkers of endothelial activation in predicting morbidity and mortality in patients with severe sepsis and septic shock in intensive care: A prospective observational study

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ABSTRACT

Introduction: Endothelial dysfunction plays an essential role in the pathogenesis of sepsis. The study aimed to illustrate the associations between the dynamic change (from day 1 to day 7) in biomarker concentration of endothelial dysfunction and outcomes in severe sepsis and septic shock in the intensive care unit (ICU).

Materials and methods: We studied 102 patients enrolled in the Beijing Chao-yang Hospital affiliated with the Capital Medical University. A receiver operating characteristic (ROC) curve were used to assess the prognostic values of the circulating adhesion Angiopoietin-2/Angiopoietin-1 ratio (Ang-2/Ang-1) and Angiopoietin-1/Tie-2 ratio (Ang-1/Tie-2), intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1 and thrombomodulin (TM). Spearman's rank correlation and a multiple regression analysis were used to assess the relationship between the change in sequential organ failure assessment (Δ SOFA) score (SOFA score at day 7 minus SOFA score at day 1) and the levels of Δ Ang-2/Ang-1 and Δ Ang-1/Tie-2 ratios, ΔsICAM-1, ΔsVCAM-1 and Δ sTM.

Results: The Ang-2/Ang-1 ratio, sICAM-1, sVCAM-1 and sTM levels significantly increased from day 1 to day 7 (all $p = 0.045$), and the Ang-1/Tie-2 ratio level markedly decreased from day 1 and day 7 ($p = 0.027$) in non-survivors. The biomarkers at Days 1 and 7 had significant prognostic value for 90-day mortality in severe sepsis and septic shock in ICU. The difference in biomarkers for endothelial dysfunction were suggested to be effective, independent predictors of changes in Δ SOFA.

Conclusions: Endothelial dysfunction may constitute an independent contributor to sepsis-associated outcomes in ICU.

1. Introduction

Sepsis is associated with high mortality as a result of complex mechanisms, including inflammation, coagulation in non-cardiac intensive care units [1]. The vascular endothelium is a target in sepsis. During sepsis, endothelial cells (ECs) are shed, vessels become leaky, cells migrate into the surrounding tissue, and inflammation and coagulation pathways are activated. The key event underlying endothelial dysfunction is the massive response of the host to inflammatory mediators and pro-coagulant factors, contributing to endothelial injury, tissue hypoperfusion, disseminated intravascular coagulation and organ dysfunction [2].

Abbreviations: Ang, angiopoietin; Tie-2, tyrosine kinase with immunoglobulin-like loop epidermal growth factor domain 2; Ang-2/Ang-1, Angiopoietin-2/Angiopoietin-1 ratio; Ang-1/Tie-2, Angiopoietin-1/Tie-2 ratio; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; TM, thrombomodulin; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; sTM, soluble thrombomodulin; ICU, intensive care unit; SOFA, sequential organ failure assessment; Δ SOFA score, SOFA score at day 7 minus SOFA score at day 1; Δ Ang-2/Ang-1 ratio, the level of Ang-2/Ang-1 ratio at day 7 minus the level of Ang-2/Ang-1 ratio at day 1; Δ Ang-1/Tie-2 ratio, the level of Ang-1/Tie-2 ratio at day 7 minus the level of Ang-1/Tie-2 ratio at day 1; Δ sICAM-1, the level of sICAM-1 at day 7 minus the level of sICAM-1 at day 1; Δ sVCAM-1, the level of sVCAM-1 at day 7 minus the level of sVCAM-1 at day 1; Δ sTM, the level of sTM at day 7 minus the level of sTM at day 1; ECs, endothelial cells; MLVECs, mouse lung vascular ECs; CIs, confidence intervals; IQR, interquartile range; CIRP, cold-inducible RNA-binding protein; H2, hydrogen; IAI, intra-abdominal infection; APACHE, Acute Physiology and Chronic Health Evaluation; ROC, receiver operating characteristic; PCT, procalcitonin; AUC, areas under the receiver operating characteristic curves

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There are diagnostic biomarkers of endothelial dysfunction, such as adhesion Angiopoietin-2/Angiopoietin-1 ratio (Ang-2/Ang-1) and Angiopoietin-1/Tie-2 ratio (Ang-1/Tie-2), intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1 and thrombomodulin (TM) [3–5]. The search for a single biomarker might ultimately be fruitless, and the combination of multiple endothelial biomarkers mentioned above should be more effective in reflecting endothelial function and predicting prognosis than single one [6].

The angiopoietin (Ang)–tyrosine kinase with immunoglobulin-like loop epidermal growth factor domain (Tie) ligand–receptor system (Ang-Tie system) is one of the most important mechanisms, which is activated in ECs during sepsis. Ang-1 and Ang-2 are secreted endothelial growth factors with divergent roles in mediating vascular quiescence [7]. Ang-1 stabilises the endothelium and inhibits vascular leakage through constitutive activation of Tie-2 receptor. In contrast, Ang-2 functions to disrupt microvascular integrity by blocking the Tie-2 receptor, which results in vascular leakage, a major mechanism of organ damage [7]. In several clinical studies of sepsis, high Ang-2 and low Ang-1 were shown to be associated with poor clinical outcome, and Ang-1 protects against organ dysfunction [8–10]. Current studies have found that high Ang-2/Ang-1 and low Ang-1/Tie-2 ratios levels are associated with the organ dysfunction and unfavourable outcome of sepsis [4,10].

In sepsis, the degree of adhesion of circulating blood cells and the relative balance between pro- and anti-coagulant activities is markedly influenced by quiescent and activated ECs [1]. When the endothelium is activated, increased luminal adhesion molecules enter the circulation in soluble form, including sICAM-1 and sVCAM-1. Circulating levels of adhesion molecules have been linked to poor outcome in sepsis [5,11]. In addition, soluble thrombomodulin (sTM) plays important roles in anti-coagulation and is released through the proteolytic activity of endothelial-bound TM [12]. With damage to the endothelium, excessive shedding of endothelial-bound TM results in a marked rise in sTM concentrations [13,14]. Therefore, sTM is proposed to be a valuable marker of endothelial damage and associated with mortality in sepsis [1,15,16].

In a large number of previous studies, biomarkers for endothelium dysfunction at admission were found to correlate with sepsis outcomes. However, there is still relatively rare study about the association between endothelial dysfunction and clinical outcomes in sepsis. Given these considerations, our aim was to investigate the correlation between the dynamic change (from day 1 to day 7) in biomarker concentration of endothelial dysfunction and the improvement of sepsis after intervention treatment.

2. Material and methods

2.1. Study design and patients

This study was conducted in the intensive care unit of the Beijing Chao-yang Hospital, affiliated with the Capital Medical University, China. Our procedures were approved by the human ethics committee of Beijing Chao-yang Hospital and, whenever possible, written informed consent form was obtained from every patient. One-hundred and two patients, hospitalised in our ICU, were continuously enrolled during the time period between 7/2014 and 12/2015. All patients met the clinical criteria based on the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference and surviving sepsis campaign guidelines [17,18] of severe sepsis (n = 48), or septic shock (n = 54).

The exclusion criteria were: (1) age < 18 years old; (2) HIV infection; (3) neutropenia, defined as < 1000 neutrophils/mm^3; (4) hypertension or constantly taking renin inhibitors; angiotensin converting enzyme inhibitors, or angiotensin II receptor antagonists; (5) chronic intake of corticosteroids; (6) recent use of unfractionated or low-molecular-weight heparin; (7) pregnancy or breast-feeding; and (8) lack of informed consent by the patients or relatives.

Data collection continued for up to 7 days, or to the point of outcomes if this occurred before 7 days. The day 7 value not only included the data from the seventh day for patients in ICU but also contained the day of death/discharge for patients who were not in ICU on day 7. Later, 90-day mortality was measured. All patients were initially treated strictly according to international guidelines for the management of sepsis. Demographic characteristics of all patients were recorded, including age, gender and associated infections.

2.2. Sample collection and measurements

Venous blood (5 mL) was collected from blood drawn for routine diagnostic procedures. Informed consent was provided prior to blood collection. The serum was immediately stored at −80 °C until further measurement. Commercial enzyme-linked immunosorbent assays were used to measure the concentration of biomarkers for endothelial dysfunction. Circulating Ang-1 and 2, Tie-2, sICAM-1, sVCAM-1 and sTM (Abcam Systems, San Francisco, CA, USA) were measured at days 1 and 7, respectively. All standards and test samples were assayed in duplicate.

2.3. Statistical analyses

Results are presented as the median (interquartile range [IQR]). Non-normal distribution of continuous variables was tested using a two-sided non-parametric Mann-Whitney *U* test. In patients, differences between survivors and non-survivors were also compared using a non-parametric two-sided Mann-Whitney test. Comparisons between groups are shown using box plot graphics. Furthermore, Spearman's rank correlation coefficient was calculated to describe correlations between the different biomarkers for endothelial dysfunction (Δ Ang-2/Ang-1 ratio, Δ Ang-1/Tie-2 ratio, Δ sICAM-1, Δ sVCAM-1, Δ sTM) and the difference of SOFA (Δ SOFA) score between days 1 and 7. A multiple regression analysis was also used to assess the relationship between Δ Ang-2/Ang-1 ratio, Δ Ang-1/Tie-2 ratio, Δ sICAM-1, Δ sVCAM-1, Δ sTM and Δ SOFA score. Differences were considered significant for two-sided $p < 0.05$, and confidence intervals (CIs) were reported at 95% for relative risks. Data were analysed using SPSS statistical software 19.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline characteristics

The 102 patients enrolled were classified assigned to severe sepsis and septic shock groups during their hospital stay. In our study, a total of severe sepsis patients were 48, 42 of whom were still on treatment on the seventh day, and the content of endothelial biomarkers were measured on the seventh day. The other 5 patients were discharged within 7 days after the improvement, and the measurement was carried out on the day of discharge. There were 54 sepsis shocks, 44 of whom were still on treatment on the seventh day, and the levels of endothelial biomarkers on seventh day were measured. The other 10 patients became aggravated and unfortunately died within 7 days. The levels on the day of death were still tested.

All 102 patients had circulating blood samples and basic characteristics collected at day 1 of ICU admission. Circulating Ang-2/Ang-1, Ang-1/Tie-2 ratios, sICAM-1, sVCAM-1, sTM and the SOFA score in ICU were significantly different between severe sepsis and septic shock. Compared to severe sepsis group, the Ang-2/Ang-1 ratio, sICAM-1, sVCAM-1, sTM and the SOFA score were significantly higher and Ang-