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Endothelial adhesion molecules and multiple organ failure in patients with severe sepsis

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ABSTRACT

Objective: To determine if serum levels of endothelial adhesion molecules were associated with the development of multiple organ failure (MOF) and in-hospital mortality in adult patients with severe sepsis.
Design: This study was a secondary data analysis of a prospective cohort study.
Setting: Patients were admitted to two tertiary intensive care units in San Antonio, TX, between 2007 and 2012.
Patients: Patients with severe sepsis at the time of intensive care unit (ICU) admission were enrolled. Inclusion criteria were consistent with previously published criteria for severe sepsis or septic shock in adults. Exclusion criteria included immunosuppressive medications or conditions.
Interventions: None.
Measurements: Baseline serum levels of the following endothelial cell adhesion molecules were measured within the first 72 h of ICU admission: Intracellular Adhesion Molecule 1 (ICAM-1), Vascular Cell Adhesion

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Intracellular Adhesion Molecule-1
Vascular Cell Adhesion Molecule-1
Vascular Endothelial Growth Factor

Molecule-1 (VCAM-1), and Vascular Endothelial Growth Factor (VEGF). The primary and secondary outcomes were development of MOF ($\geqslant$2 organ dysfunction) and in-hospital mortality, respectively.
Main results: Forty-eight patients were enrolled in this study, of which 29 (60%) developed MOF. Patients that developed MOF had higher levels of VCAM-1 (p = 0.01) and ICAM-1 (p = 0.01), but not VEGF (p = 0.70) compared with patients without MOF (single organ failure only). The area under the curve (AUC) to predict MOF according to VCAM-1, ICAM-1 and VEGF was 0.71, 0.73, and 0.54, respectively. Only increased VCAM-1 levels were associated with in-hospital mortality (p = 0.03). These associations were maintained even after adjusting for APACHE and SOFA scores using logistic regression.
Conclusions: High levels of serum ICAM-1 was associated with the development of MOF. High levels of VCAM-1 was associated with both MOF and in-hospital mortality.

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1. Introduction

Mortality rates for patients with severe sepsis and septic shock range from 40% to 60%, costing the United States health care system approximately $17 billion annually [1]. To expedite the initiation of effective treatments and thereby reduce mortality and associated costs, better methods to identify patients with severe sepsis are needed Hemodynamic parameters and laboratory tests, including lactate levels are currently used to predict multiple organ failure (MOF) in patients with sepsis; however information regarding how to detect early organ failure is limited [2,3]. Clinical deterioration and death result from a complex interaction between inflammation and coagulation that leads to organ dysfunction [4]. Vascular endothelial damage precedes organ dysfunction and plays an important role by increasing vascular permeability, promoting activation of the coagulation cascade and compromising regional perfusion in vital organs (e.g. kidneys, liver, gut, etc.) [5]. Different biomarkers have been proposed to assess vascular endothelial damage in patients with sepsis and the development of MOF and mortality [6]. Cell adhesion molecules (CAMs) have emerged as potential biomarkers that may be used to detect early endothelial injury in septic patients [7].

Vascular Endothelial Growth Factor (VEGF), Intracellular Adhesion Molecule 1 (ICAM-1), and Vascular Cell Adhesion Molecule-1 (VCAM-1) are a group of trans-membrane CAM proteins that are responsible for the cell adhesion process. These CAMs allow cells to interact with the extracellular matrix, the cytoskeleton, and other cells within the vascular endothelium, as well as other cells within the circulation [8]. ICAM-1 and VCAM-1 are present in the cell membrane of both leukocytes and the cells lining the vascular endothelium, allowing inflammatory cells to transmigrate into nearby tissues [8]. These adhesion molecules are expressed in very large quantities in patients with an uncontrolled inflammatory state such as sepsis [9]. As a result, some of these CAMs also leak into circulation, and especially after the vascular endothelial injury that occurs during sepsis, making them measurable. The value of VEGF for prediction of clinical outcomes in patients with sepsis is at present still controversial[10,11], and limited data are available in adult patients with sepsis regarding ICAM-1 and VCAM-1 levels [12]. Therefore, more studies are needed to evaluate the role of CAMs in predicting the outcomes of patients with sepsis.

Our hypothesis was that higher levels of CAMs are related to a higher incidence of MOF and in-hospital mortality. Therefore, the aim of this study was to determine the association of levels of CAMs with the development of MOF and in-hospital mortality in adult patients with severe sepsis or septic shock.

2. Material and methods

2.1. Study design

This study was a secondary analysis of the data derived from a cohort of patients admitted to the intensive care unit (ICU) with severe sepsis or septic shock at two hospitals (South Texas Veterans Health Care System and University Hospital, San Antonio, TX), between 2007 and 2012, as previously descried [13]. This study was approved by the local institutional review board (HSC20070713H), and is posted on www.clinicaltrials.gov (NCT00708799). All participants signed a consent form before entry into the study.

Table 1
Organ failure criteria.

Organ/ system	Criteria
Cardiovascular	Mean arterial pressure <65 mmHg or requirement for vasopressors or inotropes after appropriate volume resuscitation (30 mL/kg)
Respiratory	PaO_2/FiO_2 <300 or requirement for mechanical ventilation or non-invasive ventilation
Renal	Patients who receive renal replacement therapy or serum creatinine $\geqslant$354 μmol/L (4 mg/dL) or urine output <0.3 mL/kg/h
Hematologic	Prothrombin time and partial thromboplastin time >1.5–3 times the normal range or platelet count <100.000 /mm^3
Hepatic	Alanine aminotransferase and aspartate aminotransferase >100 Units/L or total plasma bilirubin >1 mg/dL (0.17 mmol/L)
Central nervous system	Glasgow coma scale score <12 points in absence of sedation

Table 2
Baseline characteristics of patients with severe sepsis stratified according to the presence of multiple organ failure (MOF) during ICU hospitalization.

Characteristic	No MOF (n = 19)	MOF (n = 29)	*p* Value
Demographic			
Male	19 (100)	27 (93)	0.60
Age, mean (IQR[a])	59 (51, 65)	58 (45, 79)	0.60
Comorbid conditions, n (%)			
Obesity	7 (37)	12 (41)	0.50
Active cancer	2 (10)	0 (0)	0.20
Prior cancer	3 (16)	5 (17)	0.60
Cardiovascular disease	7 (37)	5 (17)	0.10
Chronic heart failure	3 (16)	1 (3)	0.20
COPD	3 (16)	3 (10)	0.40
Chronic kidney disease	3 (16)	2 (7)	0.30
Depression	2 (10)	7 (24)	0.20
Diabetes mellitus	10 (53)	13 (45)	0.40
HIV infection	1 (5)	0 (0)	0.70
Hyperlipidemia	4 (17)	1 (3)	0.60
Leukemia	1 (5)	0 (0)	0.40
Liver disease	1 (5)	2 (7)	0.60
Tobacco use	6 (32)	8 (28)	0.50
Alcohol use	4 (21)	7 (24)	0.50
Asthma	1 (5)	3 (10)	0.50
Source of infection, n (%)			
Pulmonary	7 (37)	8 (28)	0.50
Urinary tract	6 (32)	10 (34)	0.30
Gastrointestinal	2 (10)	4 (14)	0.40
Skin	3 (16)	5 (17)	0.30
Endocarditis	0 (0)	1 (3)	0.90

[a] IQR, interquartile range.