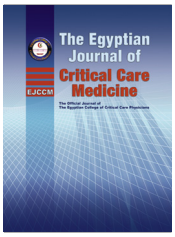
The Egyptian Journal of Critical Care Medicine (2016) xxx, xxx–xxx

The Egyptian College of Critical Care Physicians

The Egyptian Journal of Critical Care Medicine

http://ees.elsevier.com/ejccm
www.sciencedirect.com



ORIGINAL ARTICLE

# Prognostic value of vascular endothelial growth factor in sepsis syndrome

**Hazem El-Akabawy** [a,*], **Mohamed Abo Hamela** [a], **Ayman Gaber** [a], **Ahmed Abozekry** [b]

[a] *Critical Care Medicine, Cairo University, Cairo, Egypt*
[b] *Critical Care Medicine, New Kasr Al Aini Teaching Hospital, Cairo, Egypt*

Received 11 December 2015; revised 29 September 2016; accepted 16 October 2016

**KEYWORDS**

Sepsis;
VEGF;
Microalbuminuria

**Abstract** *Background:* Serum vascular endothelial growth factor (VEGF) levels are increased in sepsis.

*Purpose:* To investigate the prognostic value of the serum VEGF level in critically ill septic patients regarding the clinical course and final outcome.

*Methods:* A total of 40 critically ill septic patients were included in a prospective, randomized, single center study. All patients were subjected to the measurement of VEGF levels on admission day (VEGF1) and 48 hours later (VEGF2). CRP levels and Microalbuminuria levels were also measured on admission. APACHE IV and SOFA scores were calculated. Clinical outcome (duration of stay in the ICU, need for MV, need for inotropic/vasopressor support, need for hemodialysis, and survival) was recorded.

*Results:* In relation to healthy subjects, the mean VEGF 1&2 levels were significantly higher in the septic patients (142 + 28.98 vs 750.5 + 380.34 and 802.07 + 292.65 ng/l; $p = 0.001$ and $< 0.001$ respectively). Septic patients who required MV, inotropic/vasopressor support and hemodialysis, and also those who died had significantly higher VEGF1 levels compared to those who didn't require them ($p = 0.002$, 0.006, 0.008 and 0.001 respectively). VEGF2 level was significantly higher only in those who required inotropic/vasopressor support ($p = 0.024$). VEGF1 and 2 levels were significantly positively correlated with CRP level, Albumin/Creatinine ratio and APACHE IV score. ROC analysis of the data indicated a sensitivity of 85.15% and a specificity of 92.3% when a VEGF 1 level of 410 ng/l was taken as a predictor of ICU mortality.

*Conclusion:* The admission VEGF is a useful marker for the evaluation of septic patients.



* Corresponding author at: Critical Care Medicine Department, Kasr Alaini, Cairo University, 4-Mahmoud Samy Barody street, Alharam street, Cairo, Egypt.
E-mail addresses: hazem616@hotmail.com (H. El-Akabawy), hamela@hotmail.com (M.A. Hamela), aymangaber71@hotmail.com (A. Gaber), Drahmedcritical@yahoo.com (A. Abozekry).

Peer review under responsibility of The Egyptian College of Critical Care Physicians.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.ejccm.2016.10.002


Please cite this article in press as: El-Akabawy H et al. Prognostic value of vascular endothelial growth factor in sepsis syndrome, Egypt J Crit Care Med (2016), http://dx.doi.org/10.1016/j.ejccm.2016.10.002

## 1. Introduction

The prognosis of patients is important in risk stratification and for the efficient use of hospital resources. Predicting the outcome of patients in the intensive care environment is of particular significance to ensure that resources are used appropriately. Incidence of sepsis is increasing. Severe sepsis, which occurs when sepsis progresses to involve acute organ dysfunction, results in more than 200,000 annual fatalities, and the number of cases is projected to increase [1].

Vascular permeability increases in response to systemic inflammation mediated by endotoxin and various cytokines. Macrophages and lymphocytes can produce vascular endothelial growth factor (VEGF) [2,3]. The vascular permeability factor was isolated in 1983 [4]. VEGF was identified in 1989, and in the same year, these two substances were found to be identical [5,6].

There are seven different VEGFs (VEGF-A,-B,-C,-D,-E,-F and placental growth factor PlGF), which have different physiological and biological properties. There are at least 6 VEGF-A isoforms of different sizes (with 121,145, 165, 183, 189 and 206 amino acid residues) [7,8]. VEGFs are involved, for instance, in wound healing, cardiovascular diseases, tumour growth and progression, ocular neovascularization and inflammatory diseases such as rheumatoid arthritis. In particular, VEGF-A acts on endothelial cells, causing vasodilatation by induction of endothelial nitric oxide synthase [9]. VEGF-A also has antiapoptotic effects on endothelium [10]. More importantly, VEGF-A was found to be an important mediator of vascular permeability [5]. Also, VEGF is a potent hypoxia-induced mediator in the formation of new capillaries (angiogenesis). VEGF-induced angiogenesis was also found to play an important role in the etiology of several additional diseases associated with abnormal angiogenesis as tumor angiogenesis [11–13] and in wound repair [14].

A number of prognostication tools have been developed for prediction of outcome in the critically ill septic patients, such as scoring systems (including Acute Physiology and Chronic Health Evaluation IV ‘‘APACHE IV” [15] and The Sequential Organ Failure Assessment score ‘‘SOFA” [16]) and chemical biomarkers (including CRP [17–19], procalcitonin [20], microalbuminuria [21,22] and inflammatory cytokines as IL6 and IL8 [23]).

The aim of this work is to investigate the prognostic value of VEGF concentrations in critically ill septic patients, and also to compare this prognostic value of VEGF with other biochemical markers for the prognosis of sepsis (CRP and microalbuminuria) and with the APACHE IV and SOFA scoring systems.

## 2. Patients and methods

### 2.1. Patients

Forty patients who had been diagnosed with sepsis and were admitted to the Critical care department at Cairo university hospital from September 2013 to August 2014 were enrolled in this prospective observational single centre study. The study protocol was approved by the ethics committee. This study did not interfere with normal routine patient management.

**Inclusion criteria:** (1) Age $\geqslant$ 18 years old (2) Informed consent given by the patient or immediate relative (first degree) (3) Sepsis (ACCP/SCCM criteria) [24]: (a) Clinically suspected infection as per the treating physician or confirmed infection and (b) 2 or more of the following: Temperature $>38$ °C (100.4°F) or $<36$ °C (96.8°F), heart rate (HR) $>$ 90/min, respiratory rate (RR) $>$ 20/min or $PaCO_2 < 32$ mmHg, White blood cell count $> 12{,}000/mm^3$ or $<4000/mm3$ or $>10\%$ immature neutrophils. ***Severe sepsis*** is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. ***Septic shock*** is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. ***Sepsis-induced hypotension*** is defined as a systolic blood pressure (**SBP**) $<90$ mmHg or mean arterial pressure (**MAP**) $<70$ mmHg or a **SBP** decrease $>40$ mmHg in the absence of other causes of hypotension.

**Exclusion criteria** included trauma, burns, acute myocardial infarction and patients with a history of autoimmune disease or malignancy.

Patients who were diagnosed as having sepsis at ICU admission and did not meet any of the exclusion criteria were included into the study on the day of ICU admission, and subsequently followed up until the day of discharge or demise.

The blood samples were also collected from 10 healthy age matched subjects as a control.

### 2.2. Evaluation of patients

All included patients were subjected to the following

#### 2.2.1. Full clinical evaluation

Including a history and physical examination with a special emphasis on vital signs (BP, HR, Temperature and RR) and Glasgow coma scale (GCS); these were evaluated on the day of admission and then followed up daily (every 2 h for vital signs and once daily for GCS).

#### 2.2.2. Laboratory investigations

- **Routine Labs:** ***CBC (complete blood count):*** Hemoglobin, Hematocrit, White blood cells and platelet count, ***Coagulation profile:*** PT, PC, INR and PTT, ***Kidney Function Tests:*** Na, K, Creatinine and Urea, ***Liver Function Tests***: ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), BIL (bilirubin) and albumin and ***ABGs*** (arterial blood gases).
  These routine Labs were withdrawn on study day 1 and subsequently thereafter every day until ICU discharge or demise.
- **Labs specific for this study:** ***Total VEGF (Vascular Endothelial Growth Factor)*** [25,26]: VEGF was measured using a double-antibody sandwich enzyme-linked immune sorbent assay (ELISA) on the day of admission (VEGF1) and after 48 h i.e. on the morning of the third day (VEGF2). VEGF was added to the monoclonal antibody enzyme well, which was pre-coated with an incubated human VEGF monoclonal antibody. Then, VEGF antibodies labeled with biotin were added and combined with Streptavidin-HRP to form an immune complex, which was then incubated and washed again to remove the uncombined enzyme. After this, a chromogen solution was added, causing the color of the liquid to

Please cite this article in press as: El-Akabawy H et al. Prognostic value of vascular endothelial growth factor in sepsis syndrome, Egypt J Crit Care Med (2016), http://dx.doi.org/10.1016/j.ejccm.2016.10.002