بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / مني مغربي أحمد

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد

Impact of STAB-1 level during the neutropenic state in septic patients with haematological malignancies

Thesis
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بسم الله الرحمن الرحيم
قَالوُاسُبحَانَك لاَعلمَ لنَا إلا مَاعَلمتَناَ
إنكَ أَنتَ العَلِيمُ الحَكِيمُ
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Mohamed Gamal Mohamed Kotb

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List of abbreviations

AKI	acute kidney injury
AML	Acute myelogenous leukemia
CLP	cecal ligation and puncture
DC	dendritic cells
DIC	disseminated intravascular coagulation
ECs	endothelial cells
ED	emergency department
G-CSF	granulocyte colony-stimulating factors
HA	hyaluronan
HCC	hepatocellular cancer
HEVs	high endothelial venules
HLA-DR	human leukocyte antigen DR
HMGB1	high-mobility group box 1
ICU	intensive care unit
IFNs	interferons
IL	interleukins
ISTH	International Society on Thrombosis and Haemostasis
LPS	lipopolysaccharide
LSEC	Liver sinusoidal endothelial cells
MDSCs	myeloid-derived suppressor cells
MFG-E8	milk fat globule EGF factor 8
NAD	nicotinamide adenine dinucleotide
NETs	neutrophil extracellular traps
PS	phosphatidylserine
STAB-1	Macrophage Stabilin-1
TF	tissue factor
TGN	Trans Golgi network
TLR	Toll-like receptor
TNF-α	tumor necrosis factor alpha

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ABSTRACT

Background; Sepsis is a complex clinical syndrome characterized by systemic inflammation, vascular leakeage and organ failure representing a major therapeutic burden. Oncology patients are considered a high-risk patient population, especially with the higher risk of sepsis, most likely due to their immunosuppressed state. **Aim and objectives;** to measure serum levels of stablin 1 in adult patients with hematological malignancies during the neutropenic state who had any form of clinical or laboratory diagnosis of sepsis, And to correlate its level with other diagnostic and prognostic parameters, **Subjects and methods**; This prospective study was carried out on 40 adult patients with hematological malignancies with sepsis in neutropenic state. The patients were admitted to Clinical Hematology and Oncology Division, Internal Medicine Department, Ain Shams University in comparison to 15 age and sex matched control healthy subjects, **Result;** By using ROC-curve analysis, STAB-1 level determines patients with hematological malignancies with sepsis in neutropenic state with sensitivity and specificity was 80% and 93.3% respectively when the cutoff point was >.31, **Conclusion;** STAB-1 level increases in patients with hematological malignancies with sepsis in neutropenic state. STAB-1 level is an effective measure to determine patients with hematological malignancies with sepsis in neutropenic state.

INTRODUCTION

Sepsis is a complex clinical syndrome characterized by systemic inflammation, vascular leakeage and organ failure representing a major therapeutic burden **(Lelubre, Vincent, 2018)**.

Vascular leakage is an important mechanism in pathogensis and progression of sepsis process which occure due to disruption of the vascular barrier by inflammatory stimuli .Maintenance of vascular integrity is supported by the efficient removal of apoptotic endothelial cells (**Soon et al., 2016; Russell et al., 2018)**.

The phagocytic clearance of damaged cells by macrophages, a process termed efferocytosis, induces resolution of inflammation and suppression of pro-inflammatory cytokines **(Kourtzelis et al., 2017; Fullerton et al., 2013)**.

Macrophage Stabilin-1 (STAB-1) which is a phagocytic receptor mediating efferocytosis protects against disruption of vascular integrity in the course of sepsis and promotes clearance of apoptotic vascular endothelial cells damaged by severe inflammation **(Lee et al., 2018)**.

It was found that genetic deletion of STAB-1 decreased the survival of septic mice in the model of cecalligation and puncture. Decreased sepsis survival in STAB-1 deficiency was associated with diminished efferocytosis, increased vascular permeability and enhanced organ dysfunction **(Lee et al., 2014)**.

Also it was found that the pro-inflammatory mediator high-mobility group box 1 (HMGB1) inhibit STAB- 1-dependent efferocytosis of apoptotic cells, and blockade of HMGB1 with a neutralizing antibody

improved the phagocytic capacity of macrophages and reduced sepsis Mortality **(Orlova et al., 2007; Lotze and Tracy et al., 2005).**

Palani et al demonstrated that STAB-1 on monocytes suppresses the activation of Th1 lymphocytes; thus, STAB-1 may also exert an immunosuppressive action. In addition, STAB-1 regulates lymphocyte migration and inflammatory cell recruitment **(Palani et al., 2016).**

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*Aim Of The Wor*k

The aim of the present study is to measure serum levels of stablin 1 in adult patients with hematological malignancies during the neutropenic state who had any form of clinical or laboratory diagnosis of sepsis, And to correlate its level with other diagnostic and prognostic parameters.

Chapter (1)

Sepsis

Sepsis is a life-threatening clinical condition with extensive physiological and biochemical abnormalities. The Third International Consensus (Sepsis-3) currently defines sepsis as "organ dysfunction caused by a dysregulated host response to infection", emphasizing for the first time the crucial role of the innate and adaptive immune response in the development of the clinical syndrome **(Singer et al., 2016).**

Approximately 49 million people are affected by sepsis every year and it is estimated that 11 million deaths are caused by the syndrome, accounting for up to 19.7% of all deaths worldwide **(Rudd et al., 2020).** Globally, mortality rates seem to be declining on average, however, up to 25% of patients still succumb to sepsis. In septic shock, a subgroup of sepsis characterized by profound circulatory, cellular and metabolic abnormalities, the hospital mortality rate approaches 60% **(Vincent et al., 2019).**

Comprehensively defining "sepsis" has been subject of constant development and refinement over the last decades. Although our understanding of origin, pathophysiology, and immunological mechanisms of sepsis has made progress during the last three decades, our options of successful and specific therapeutic interventions remain restricted to non-existent **(Jarczak et al., 2021).**

Only timely fluid resuscitation and early administration of broad-spectrum antibiotics have been shown to reduce mortality. A decisive factor is the time of correct diagnosis and the initiation of causal,

supportive, and adjunctive measures. This implies that increasing awareness of sepsis and the promotion of quality improvement initiatives in the field of sepsis effectively improve patient survival, together with the development of novel diagnostics and interventions **(Levy et al., 2014).**

Proposed criteria for sepsis and septic shock

This proposal stems from the 2015 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) **(Singer et al., 2016),** which considers infection to be an interaction between a host and a pathogen that induces a local or systemic host response.

Sepsis

- Life-threatening organ dysfunction owing to a dysregulated host response to infection
- Onset marked by the beginning of any organ dysfunction remote from the site of infection

Septic shock

- A subset of sepsis in which underlying circulatory and cellular–metabolic abnormalities are profound enough to substantially increase mortality
- Operationally defined as requiring vasopressor therapy to maintain a mean arterial blood pressure of >65 mmHg and an increased plasma lactate level of >2 mmol per l