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قَالُوا سُبْحَانَكَ لاَ عِلمَ لَنَا إِلاّ مَا

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SERUM SOLUBLE TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS-1 (STREM-1) AS A DIAGNOSTIC AND A PROGNOSTIC MARKER IN SEPSIS EVOLUTION IN COMPARISON TO PROCALCITONIN AND INTERLEUKIN-6

Thesis

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List of Abbreviations

ACCP	American College of Chest Physicians.
ALT	Alanine aminotransferase.
ANOVA	Analysis of Variance.
APACHEII	Acute Physiology And Chronic Health Evaluation II.
APC	Activated Protein C
ARDS	Adult Respiratory Distress Syndrome.
AST	Aspartate aminotransferease.
AUC	Area Under the Curve.
BSF-2	B Cell Stimulating Factor 2
BUN	Blood Urea Nitrogen.
CBC	Complete Blood Count.
Cr	Creatinine.
CRP	C Reactive Protein
DAP12	Transmembrane adapter protein
DVT	Deep Venous Thrombosis.
FiO_2	Inspired Oxygen fraction.
GI	Gastrointestinal
IFNB2	Interferon B2
IL6	Interleukin 6
INR	International Normalized Ratio.
KDa	Kilo Dalton.
LPS	Lipopolysaccharides.

MAP	Mean Arterial Pressure.
MGI-2A	Macrophage-Granulocyte Inducing factor 2A.
MHC	Major Histocompatibility
MODS	Multiple Organ Dysfunction syndrome.
NF-κB	Nuclear factor κB.
NOD1	NOD2: Nucleotide-Binding Oligomerization Domain
$PaCo_2$	Arterial Carbon dioxide Partial pressure.
PAMPs	Associated molecular patterns
PDGF	Platelet derived growth factor
PRRs	Pattern recognition receptors
PT	Prothrombin Time.
PTT	Partial Thromboblastin time.
ROC curve	Receiver Operating Characteristic curve.
SCCM	Society of Critical Care Medicine.
SIRS	Systemic Inflammatory Response Syndrome.
SOFA	Sequential Organ Function Assessment.
SPSS	Statistical Package of Social Sciences.
sTREM-1	Soluble Triggering Receptor Expressed on Myeloid Cells 1
Th1	T helper cells
TLR	Toll Like Receptors.
TNF- α	Tumor Necrosis Factor α.
WBCs	White Blood Cells.
ZAP70	zeta chain associated protein 70

Introduction

Sepsis, severe sepsis and septic shock are currently among the most common causes of morbidity and mortality in intensive care, and their incidences have increased during the past decade as the population has aged. The need to diagnose the condition upon admission had warranted attention long time ago as the administration of antimicrobials in the first 4 hours had marked influence on the outcome ***(Medzhitov, 2001).***

The focus of infection is sometimes difficult to ascertain, cultures might take longer time to be available, many microorganisms require sophisticated techniques for their analysis that is why the need for an early biologic marker had evolved and became the trend in the past few decades. ***(Medzhitov, 2001).***

The administration of antimicrobials in the sepsis had markedly influenced the outcome, in one setting, administration within the first 4 hours had marked decrease in morbidity and mortality (statistical and clinical significance), and moreover the delay in antimicrobial therapy might increase the likelihood of mortality by 7.6% for each hour delay in another setting.***(Lanier, 1998)***

Various markers had been proposed for diagnosis of the septic syndrome e.g. procalcitonin, C-reactive protein

CRP,…etc, on the other had some were appointed as prognostic e.g. Interleukin 6 (IL6), various tumor necrosis factors, IL8, IL10 ***(Lanier, 1998)***.

The need for a reliable marker with which diagnosis and prognosis can be predicted warrants clinical attention.

Aim of the Work

The present study focused on the power of the soluble triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1) -serum levels estimation- to procalcitonin (PCT) in the early and reliable diagnosis of severe infections in intensive care setting in patients with sepsis. Moreover we were aiming at defining the power of sTREM-1 as a prognostic marker to IL6 and its relation to the patients' final outcome of the sepsis cascade.

Review of Literature

Introductory period:

The word ‘‘sepsis’’ has its origin from the word ***‘‘σ΄ηψις’’***, which is the original Greek word for decomposition or putrefaction, and had been used in that context since before Hippocrates. However, although the word, sepsis, had been used for more than 2700 years, it is only relatively recently that the pathophysiology of sepsis is being partially understood ***(Schottmueller et al., 1914, Vincent et al., 2006).***

What is SIRS?

In 1991, a Consensus Conference was held by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) to create a ‘‘set of definitions that could be applied to patients with sepsis and its sequelae ***(ACCP-SCCM Consensus Conference, 1992)***.

The goal of the conference was to provide a ‘‘framework’’ to define the systemic inflammatory response to infection, and by so doing to improve the early diagnosis of sepsis, thus allowing earlier therapeutic intervention.

It had been recognized that the same systemic response seen in patients with severe infections, could also occur in patients without infection but with other inflammatory processes, e.g. pancreatitis, multiple trauma, ischemia, burns,

etc. and the consensus conference believed it was necessary to introduce new terminology to define such patients. The key aspect of the consensus conference definitions was, therefore, the introduction of the term ***Systemic Inflammatory Response Syndrome*** or SIRS to define this phenomenon. SIRS was defined as being the presence of more than one of four clinical criteria:

1. Body temperature greater than 38°C or less than 36°C
2. Heart rate greater than 90 beats/min
3. Respiratory rate greater than 20 breaths/min or hyperventilation with a PaCO2 less than 32 mmHg.
4. White blood cell count >12000/mm^3, <4000/mm^3, or with >10% immature neutrophils (Band cells)

The SIRS approach was rapidly adopted by many and has been widely used to define populations of patients for inclusion in clinical trials. However, not all have considered the SIRS criteria useful, arguing that they are too sensitive and non-specific to be of any real use in clinical diagnosis or in the clinical trial setting ***(Vincent, 1997)***.

Indeed, most intensive care unit (ICU) patients and many general ward patients meet the SIRS criteria ***(Sprung et al., 2006)*** in the recent Sepsis Occurrence in acutely ill Patients (SOAP) study, 93% of ICU admissions had at least two SIRS criteria at some point during their ICU stay ***(Sprung et al., 2006)***. In addition, a ‘‘diagnosis’’ of SIRS provides no real