Prognostic Value of Lactate / Albumin Ratio Combined with APACHE II, SAPS II and SOFA Score for Predicting Mortality in Critically Ill Patients with Septic Shock

Thesis

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LIST OF ABBREVIATIONS

ACTH	**:**	Adrenocorticotropic hormone
AF	**:**	Atrial fibrillation
AKI	**:**	Acute kidney injury
APACHE II	**:**	Acute Physiology and Chronic Health Evaluation II
ARDS	**:**	Acute respiratory distress syndrome
ATN	**:**	Acute tubular necrosis
AUC	**:**	Area under the curve
BNP	**:**	Brain natriuretic peptide
CBC	**:**	Complete Blood Count
CRP	**:**	C-reactive protein
CT	**:**	Computer tomography
DBP	**:**	Diastolic blood pressure
DIC	**:**	Disseminated intravascular coagulation
Dobut	**:**	Dobutamine
Dop	**:**	Dopamine
ECG	**:**	Echocardiography
ED	**:**	Emergency department
ESICM	**:**	European Societies of Critical and Intensive Care
GCS	**:**	Glasgow coma scale
HR	**:**	Heart rate
ICU	**:**	Intensive care unit
INR	**:**	International normalized ratio
IV	**:**	Intra venous
L/A	**:**	Lactate/ albumin
LAR	**:**	Lactate/ albumin ratio
LDH	**:**	Lactate dehydrogenase
LVEF	**:**	Left ventricular ejection fraction
MEWS	**:**	Modified Early Warning Score

MODS	**:**	Multi-organ dysfunction syndrome
MV	**:**	Mechanical ventilation
NE	**:**	Norepinephrine
NEWS	**:**	National Early Warning Score
NPV	**:**	Negative predictive value
OR	**:**	Odds ratio
PPV	**:**	Positive predictive value
q SOFA	**:**	Quick Sequential Organ Failure Assessment
RCTs	**:**	Randomized controlled trials
ROC	**:**	Receiver operating characteristic curve
RR	**:**	Respiratory rate
S.cr	**:**	Serum creatinine
SAPS II	**:**	Simplified Acute Physiologic Score II
SIRS	**:**	systemic inflammatory response syndrome
SOFA	**:**	Sequential Organ Failure Assessment
TCP	**:**	Thrombocytopenia
TNF-α	**:**	Tumor necrotizing factor alpha
UOP	**:**	Urine output
UTI	**:**	Urinary tract infections
WBCs	**:**	White blood cells
WHO	**:**	World Health Organization

ABSTRACT

Background: Despite all worldwide efforts towards sepsis, more than 5.3 million patients die annually. Till now, there is no parameter or score to detect mortality in septic patients precisely.

Objectives: The aim of this study was to evaluate the prognostic performance of the lactate/albumin (L/A) ratio when combined with APACHE II score,,SOFA score and SAPS II for predicting 28-day mortality in critically ill patients with septic shock.

Patients and Methods: After approval of the Medical Ethics Committee of Ain Shams Faculty of Medicine, an informed consent was taken from the patient or next of kin to include his/her data in this study. All patients who were admitted to the intensive care units (ICUs) with septic shock from 1st of September, 2019 to 30th of March, 2020 were assessed for enrollment in this study.

Results: In this prospective observational study, 100 adult patients of both sexes with septic shock were enrolled. They were categorized into two groups according to the primary endpoint (outcome) "28-days mortality". Sixty-one patients (61%) died (non-survivors group) and thirty-nine patients (39%) survived (survivors group). The most significant factors which affecting the mortality were LAR, SOFA score on admission, APACHE II, and SAPS II score. Prediction performance of the four variables for estimating 28 days mortality**.** When combined LAR + SOFA , LAR + APACHE, LAR + SAPS II, Overall score the ROC (AUROC, 0.867,0.847,0.849,,0.899 respectively) was the highest, compared to the other single models and lower cutoff (>0.48, >0.53, >0.42, >0.47 respectively)in comparison to single scores. Moreover, the overall score (including the 4 parameters together) gave the best predictive value for 28 day mortality

Conclusion: Lactate/Albumin ratio combined with APACHI II, SOFA and SAPS scores gave the best predictive value for 28 day mortality in septic shock patients, when compared with each separate score

Recommendations: combined LAR + SOFA , LAR + APACHE, LAR + SAPS II, Overall score recommended to use to predicthospital mortality, Further research on large sample sizeto study therisk stratification and implementing new scores using the lactate/albumin ratio (LAR) is needed.Simple, available and cheap markers should be used in developing new prediction scores.

Keywords: Lactate / Albumin Ratio- APACHE II - SAPS II - SOFA Score – Mortality- Septic Shock patients.

INTRODUCTION

Despite all worldwide efforts, more than 5.3 million patients die annually from sepsis. It still has a great economic impact due to direct medical costs and the social repercussions resulting from the physical, psychological, and cognitive disabilities of the survivors. **(Scott, 2017)**.Definitions of sepsis have been changed dramatically **(Marshall, 2016)**.The North American (SCCM) and European Critical Care and Intensive Care Societies (ESICM) updated the definition of sepsis to standardize the terminology, improve early detection, and increase consistency in the inclusion of patients in clinical trials**.** Sepsis has been defined as "life-threatening organic dysfunction caused by an unregulated response to infection." (**Singer et al., 2016)**

For predicting mortality in critically ill septic shockpatients, several parameters have been used such as APACHE II**score (Pollak et al., 1991);** SOFA score (**Vincent et al., 1996; Moreno et al., 1999)**,SAPS II score (**Adamzik et al., 2011;),** lactate (**Levy, 2011)**, albumin (**Caironi et al., 2015)**and lactate to albumin ratio (LAR) **(Wang et al., 2015; Choi et al., 2016).** All these parameters and scores can predict mortality, to variable degrees, in critically ill patients with septic shock. But, no one parameter is the gold standard for detecting mortality. If we combine these scores together, can prediction of mortality in such patients be improved?

AIM OF THE WORK

The aim of this study was to evaluate the prognostic performance of the lactate/albumin (L/A) ratio when combined with SOFA score and SAPS II for predicting 28-day mortality in critically ill patients with septic shock.

REVIEW OF LITERATURES

Definitions of sepsis have changed dramatically and have been source of reflection ***(Marshall, 2016)***. The first mention of sepsis was in some Egyptian papyri (> 3500 years ago) ***(Kempker & Martin, 2016)***.

The term "sepsis" comes from the Greek; it is found in Homer's Iliad and was used in the Hippocratic body ***(Botero & Pérez, 2012; Kempker & Martin, 2016)*** The Greeks used this term to describe decay or putrefaction. Then, the signs of inflammation and organ dysfunction were reported ***(Vincent et al., 2016)***. When microorganisms were identified, sepsis was considered an infection associated with these germs ***(Marshall, 2016)***.

The first universal definition of sepsis was published in **1992** by **Bone and his colleagues**. In this consensus, the definition of sepsis was simplified as the host's inflammatory response to infection. Then, the criteria of SIRS (systemic inflammatory response syndrome) was defined, by the presence of two or more of the following criteria: temperature > 38 or < 36°C, heart rate > 90 beats.min^{-1}, respiratory rate >20 breaths.min^{-1} or hyperventilation with a PaCO2 < 32 mmHg, leukocytes >12,000 or < 4000 or with more than 10% immature neutrophils ***(Bone et al., 1992)***

In **2001**, another consensus effort was made, and sepsis was defined as "a clinical syndrome defined by the presence of both infection and systemic inflammatory response syndrome". The poor specificity of SIRS in identifying patients with sepsis was accepted. Then, the list of clinical and paraclinical criteria was expanded to optimize the clinician's approach. These changes improved the sensitivity, but with lower specificity ***(Levy et al., 2003)***.

Then, sepsis was defined as "infection plus some of the following criteria: hyperthermia or hypothermia, tachycardia or tachypnea, altered mental status, edema or positive fluid balance, hyperglycemia (no history of diabetes), leukocytosis or leukopenia, elevated C-reactive protein or procalcitonin, hypotension, low mixed venous saturation or high cardiac index, hypoxia, oliguria or elevated creatinine, coagulation abnormalities, ileus, thrombocytopenia, elevated bilirubin, elevated lactate, and slow capillary filling."***(Levy et al., 2003)***

The definition and criteria were based on the opinion of experts who tried to provide simple and universal tools to allow establishing clinical diagnosis of sepsis syndromes at the first look to patients. These criteria were not specific for infection (not conclusive) so, they should be interpreted with relevant clinical situation ***(Dellinger et al., 2013)***

The North American (SCCM) and European Critical Care and Intensive Care Societies (ESICM) updated the definition of sepsis to standardize the terminology, improve early detection, and increase consistency in the inclusion of patients in clinical trials. After several meetings, they published a new definition of sepsis and septic shock in 2016 ***(Singer et al., 2016)***. Now, sepsis is officially defined as "life-threatening organic dysfunction caused by an unregulated response to infection." This underscores the widely held view that the presence of a systemic response does not necessarily reflect an inappropriate, unregulated host response and that non-regulation is best identified by organ dysfunction. Sepsis was emphasized without organic dysfunction, hypotension, or hypoperfusion is a very different entity from septic shock and may not require an aggressive approach ***(Singer et al., 2016)***

For these new definitions, they considered the following: Sepsis is the primary cause of death from infection, especially when it is not recognized and treated properly. Sepsis is a syndrome generated by pathogen and host factors that differs from infection by an aberrant or unregulated host response and by presence of organic dysfunction. The organic dysfunction induced by sepsis may be hidden, and its presence should be considered in any patient with infection. Also, as an unrecognized infection can cause organic dysfunction, any organ dysfunction should warn about possible underlying infection. The clinical and biological

phenotype of sepsis may be altered by pre-existing disease, comorbidities, medications, or interventions. Specific infections can lead to localized organ dysfunction without generating an unregulated host response ***(Singer et al., 2016)***.

Multi-organ dysfunction is not distributed uniformly across systems. The most frequently affected systems are the cardiovascular and respiratory in about 50% of patients. Renal system is affected in about 30% of patients. Other organ systems are affected with lower frequencies. Due to its complexity and misunderstood pathophysiology, organ dysfunction may persist for weeks. So, it affects hospital and ICU stay, ventilatory support and mortality rate ***(McConnell & Coopersmith, 2016; Singer et al., 2016)***

Respiratory disturbances may include capillary leakage and increased alveolar permeability causing non-cardiogenic pulmonary edema, with hypoxemia and increased pulmonary elastance. Plain chest X-ray or CT scan can help diagnosis. Acute respiratory distress syndrome (ARDS) occurs if blood oxygenation is severely compromised. ***(Angus & Van der Poll, 2013)***

Cardiovascular disturbances in sepsis include atrial conduction abnormalities, ventricular myocardial injury, decreased left ventricular ejection fraction (LVEF), and ventricular dilatation. These abnormalities can be detected by

ECG, echocardiography, and high levels of brain natriuretic peptide (BNP) or troponins T or I. Clinically these can manifest as atrial fibrillation (AF) with rapid ventricular response, hypotension, and/or shock state ***(Gotts & Matthay, 2016)***

Septic **encephalopathy** usually manifests as altered mentation or delirium, which is difficult to distinguish from ICU delirium. Its pathophysiology is unclear. Brain radiography detects no abnormalities. Electroencephalography only reports non-specific diffuse encephalopathy ***(Gotts & Matthay, 2016)***.

The most common initial prerenal hypotension or shock leads to intrarenal acute tubular necrosis (ATN), which is manifested clinically as decreased urine output and raised serum creatinine, with muddy brown granular casts in urine analysis. This can progress into acute **kidney** injury (AKI) of different severities. In its most severe form (oliguric failure), renal replacement therapy (RRT) is required. Common presentations of **gastrointestinal dysfunction** are paralytic ileus and diarrhea. However, diarrhea can be related to other causes as antibiotics or Clostridium difficile infections. Liver enzymes may demonstrate a sepsis induced cholestatic pattern ***(Gotts & Matthay, 2016)***

Most common **coagulation abnormality** is disseminated intravascular coagulation (DIC), manifested by thrombocytopenia, (TCP), prolonged international normalized ratio (INR) and prolonged partial thromboplastin time (PTT) ***(Gotts & Matthay,***

2016). **Endocrine** functions are clearly affected in sepsis. The most frequent disturbances are insulin resistance, low response of adrenals to adrenocorticotropic hormone (ACTH), and transient central hypothyroidism. These manifest as hyperglycemia, relative adrenal insufficiency, and euthyroid sick syndrome ***(Angus & Van der Poll, 2013; Gotts & Matthay, 2016)***

Pathophysiology

Over years, pathophysiology has made the diagnosis of sepsis more difficult. High mortality rate led to the need for early diagnosis that would allow for implementation of more interventions in no time. This forced researchers to make it easier for the physician to make early diagnosis. Although there are about 2000 biomarkers, but no standard diagnostic one for sepsis ***(Shankar-Hari et al., 2015; Abraham, 2016)***.

In sepsis, endothelial dysfunction causes leukocyte adhesion, coagulation activation, vasodilation, and loss of barrier function leading to vascular leakage and tissue edema. ***(Klingensmith & Coopersmith, 2016)***. Also, bacterial translocation increases the permeability of the intestinal epithelium increases, which can progress into multi-organ dysfunction ***(Singer, 2014)***.

Activation of the innate immune system, particularly macrophages is the key cellular event in sepsis. The binding of pathogen-associated molecular patterns (lipopolysaccharide) or