Evaluation of Red Cell Distribution Width as a Prognostic Factor in Patients with Severe Sepsis

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List of Abbreviations

ACCP	:	American College of Chest Physicians
AIDS	:	Acquired immune deficiency syndrome
AMUH	:	Alexandria Main University Hospital
APACHE II	:	Acute Physiology and Chronic Health Evaluation II
APC	:	Activated protein C
ARDS	:	Acute respiratory distress syndrome
AUCs	:	Area under the curves
CARS	:	Compensatory anti-inflammatory response
CD4	:	cluster of differentiation 4
CDC	:	Centers for Disease Control
CKD	:	Chronic kidney disease
COPD	:	Chronic Obstructive Pulmonary Disease
CRP	:	C-reactive protein
CVP	:	Central venous pressure
DIC	:	Disseminated intravascular coagulation
DM	:	Diabetes mellitus
ED	:	Emergency department
ESICM	:	European Society of Intensive Care Medicine
Fio2	:	Fraction of inspired oxygen
H2RA	:	H2 receptor antagonists
HIV	:	Human immunodeficiency virus
HLA	:	Human leukocyte antigen
HTN	:	Hypertension
ICU	:	Intensive care unit
IHD	:	Ischemic heart disease
IL-1	:	Interleukin 1
IL-10	:	Interleukin 10
IL-4	:	Interleukin 4
IL-6	:	Interleukin 6
LMWH	:	Low molecular weight heparin

LPS	:	Lipopolysaccharide
M.V	:	Mechanical ventilation
MAP	:	Mean arterial pressure
MCV	:	Mean corpuscular volume
MODS	:	Multiple Organ Dysfunction Score
MOF	:	Multiple organ failure
NE	:	Norepinephrine
NIV	:	Noninvasive mask ventilation
NMBAs	:	Neuromuscular blocking agents
P_aCO_2	:	Partial pressure of carbon dioxide
PAMPs	:	Pathogen-associated molecular patterns
PaO_2	:	Partial pressure of oxygen
PEEP	:	Positive end-expiratory pressure
pH	:	Blood acidity
PRR	:	Pattern recognition receptors
RBC	:	Red blood cell
RDW	:	Red blood cell distribution width
ROC	:	Receiver operating characteristic curve
SaO_2	:	Oxygen saturation
SAPS II	:	Simplified Acute Physiology Score II
SCCM	:	Society of Critical Care Medicine
SGOT	:	Serum glutamic oxaloacetic transaminase
SGPT	:	Serum glutamic-pyruvic transaminase
SIRS	:	Systemic inflammatory response syndrome
SOFA	:	Sequential Organ Failure Assessment
SSC	:	Surviving Sepsis Campaign
TNF-α	:	Tumor necrosis factor alpha
TPN	:	Total parenteral nutrition
UFH	:	Unfractionated heparin
UTI	:	Urinary tract infection
VTE	:	Venous thromboembolism
WBC	:	White blood cells

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Introduction

Sepsis is life threatening organ dysfunction caused by dysregulated host response to infection **(Singer et al., 2016)**. Early classification of patients presenting with sepsis by means of objective scoring systems is desirable to determine the prognosis of patients However, none of the existing scoring systems has fulfilled all expectations. The most commonly used scoring system is The Sequential Organ Failure Assessment score, or just SOFA score, is used to track a patient's status during the stay in an intensive care unit (ICU) The SOFA score is a scoring system to determine the extent of a person's organ function or rate of failure (**Vincent et al., 1996)**. Assume baseline SOFA score of 0 in patients without known preexisting organ dysfunction while SOFA score ≥ 2 points associated with overall mortality risk of about 10% in general hospital population with suspected infection.

While septic shock **(Singer et al., 2016)** known as sepsis with underlying circulatory, cellular and metabolic abnormalities severe enough to substantially increase mortality, clinically defined as persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mm Hg and serum lactate level ≥ 2 mmol/L (18

mg/dL) despite adequate volume resuscitation associated with hospital mortality ≥ 40%.

The red blood cell distribution width (RDW) represents an index of the heterogeneity of the erythrocytes (anisocytosis), which is calculated by dividing the standard deviation of erythrocyte volume by the mean corpuscular volume (MCV) and multiplying by 100 to express the result as a percentage **(Morris et al., 2001)**.

For several decades, RDW has been typically used in combination with the MCV to differentiate the cause of underlying anemia in clinical practice **(Demir et al., 2002)**.

The mechanism of elevated RDW in these patients with sepsis is not known, But it has been suggested that inflammatory process is associated with elevated RDW and it has been reported that elevated RDW is associated with inflammatory markers such as interleukin 6 and tumor necrosis factor and pro-inflammatory cytokines could suppress the maturation of RBCS and decrease the half-life of RBCS which in turn results in elevated RDW **(Bazick et al., 2011)**.

Sepsis has a great impact on CBC result and red cell distribution width (RDW) is widely available to clinicians because it is routinely reported as part of the complete

blood count. Recently, highly significant associations have been described between RDW value and all causes of non-cardiac and cardiac mortality in patients with coronary artery disease, acute and chronic heart failure, peripheral artery disease, stroke, pulmonary embolism, and pulmonary artery hypertension **(Felker et al., 2007)**. Moreover, several studies have reported that RDW shows the predictive value of all-cause mortality in critically ill or intensive care unit (ICU) patients **(Bazick et al., 2011)**.

Aim of the Work

The aim of the work is to evaluate the RDW as a prognostic marker for septic patients regarding mortality, length of stay and duration of mechanical ventilation.

Review of Literature

Infectious diseases are a global health problem, causing many deaths per year. Respiratory infections as well as diarrhea, malaria, measles, and HIV/AIDS are major causes of morbidity and mortality worldwide. Sepsis is also one of the world's leading causes of death with at least 19 million cases every year, the majority in low- and middle-income countries **(Adhikari et al., 2010).**

The incidence is rising for various reasons. Even with appropriate antibiotics, immediate fluid resuscitation, and intensive care, patients can quickly deteriorate into septic shock leading to multiple organ failure and death. Some patients die within the first days of the early acute inflammatory phase, but the majority die after several days from secondary infections caused by profound immuno-suppression. The pathophysiology of sepsis, where many different immune cells, inflammatory mediators, and coagulation factors are involved, remains incompletely understood **(Baker et al., 2011).**

Many of the signs and symptoms that are associated with infectious diseases are a direct manifestation of the host immune response. These signs result from different

leukocytes and their metabolites in the immune system, which attempt to kill the invading pathogen. For the host, the challenge with infections is to recognize the foreign invaders and to direct the appropriate immune response effectively without inflicting self-damage. The body uses many different mechanisms to avoid such inappropriate responses, but occasionally this mechanism fails—causing severe tissue damage and death **(Angus et al., 2013).**

Risk factors for sepsis and septic shock are many and well-known, including underlying health status (e.g., the acquired immunodeficiency syndrome (AIDS) and chronic obstructive pulmonary disease (COPD), cancer), age and the use of immunosuppressive therapy **(Angus et al., 2001).**

Definitions

The Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) proposed a new definition of sepsis, termed Sepsis-3. The new proposal defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection **(Seymour et al., 2016)**. The new definition abandoned use of host inflammatory response syndrome criteria (SIRS) in identification of sepsis and eliminated the term severe sepsis.

An earlier sepsis definition, Sepsis-1, was developed at a 1991 consensus conference **(Bone et al., 1992)** in which SIRS criteria were established. Four SIRS criteria were defined, namely tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20 breaths/min), fever or hypothermia (temperature >38 or <36 ℃), and leukocytosis or leukopenia, (white blood cells >1, 2000/mm3, <4, 000/mm3). Patients who met two or more of these criteria fulfilled the definition of SIRS, and Sepsis-1 was defined as infection or suspected infection leading to the onset of SIRS. Sepsis complicated by organ dysfunction was termed severe sepsis, which could progress to septic shock, defined as "sepsis-induced hypotension persisting despite adequate fluid resuscitation." A 2001 **(Levy et al., 2003)** Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) recognized the limitations with these definitions, but did not offer alternatives due to a lack of supporting evidence. However, they did expand the list of diagnostic criteria, resulting in the introduction of Sepsis-2. Therefore, in order to be diagnosed with sepsis under the Sepsis-2 definition, as with Sepsis-1, an individual must have at least 2 SIRS criteria and a confirmed or suspected infection **(Vincent et**