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DUJE BJELIĆ

ASSESSMENT OF DIAGNOSTIC SENSITIVITY OF VARIOUS DETECTION TOOLS AND BIOMARKERS FOR THE IDENTIFICATION OF SEPSIS/SEPTIC SHOCK AT ICU ADMISSION

Diploma thesis

Academic year: 2019/2020

Mentor:

Prim. Assist. prof. Mladen Carev, MD, PhD

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LIST OF ABBREVIATIONS

ACTH - Adrenocorticotropin hormone
AKI - Acute kidney injury
APACHE II – Acute physiology and chronic health evaluation II
BBB - Blood brain barrier
C5a - Complement factor 5a
CAM - Confusion assessment method
CD4+ - Cluster of differentiation 4+
CD8+ - Cluster of differentiation 8+
CLRs - C-type lectin receptors
CNS - Central nervous system
CRH - Corticotropin-releasing hormone
CRP - C-reactive protein
DAMPs -Danger associated molecular patterns or alarmins
DIC - Disseminated intravascular coagulation
DNA - Deoxyribonucleic acid
EPIC - European prevalence of infection in tensive care
ESICM - European Society of Intensive Care Medicine
EWS - Early Warning score
FMLP - N-formyl methionyl-leucyl-phenylalanine
HIV - Human immunodeficiency virus
HMGB-1 - High mobility group box-1 protein
ICU - Intensive care unit
IL - Interleukin
IRF - Interferon regulatory factor
LBP - lipopolysaccharide-binding protein
MEDS – Mortality in the emergency department score
MODS - Multiple organ dysfunction
MyD88- Myeloid differentiation primary response 88
NEWS2 - National Early Warning Score 2
NF-κβ - Nuclear factor-κβ
NLRs - NOD-like receptors
NO - Nitric oxide
PAMPs -Pathogen-associated molecular patterns
PCT - Procalcitonin
PRRs - Pattern recognition receptors
RIG - retinoic acid-inducible gene
RLRs - RIG-I-like receptors
S/SS - Sepsis and septic shock
SBP - Systolic blood pressure
SCCM - Society of Critical Care Medicine
SIGIRR - Single-immunoglobulin interleukin IL-1 receptor-related molecule
SIRS - Systemic inflammatory response syndrome
SOCS - suppressor of cytokine signaling
SOFA - Sequential organ failure assessment
TLR4 -Toll-like receptor 4
TLRs - Toll-like receptors
TNF-a- Tumor necrosis factor alpha
TOLLIP - Toll-interacting protein
TREM-1 - Myeloid cells expressing triggering receptor-1
qSOFA - Quick Sequential Organ Failure Assessment

1. INTRODUCTION

1.1. Sepsis and septic shock

1.1.1. Definition

The word sepsis is derived from the Greek word for "decomposition" or "decay," and ever since its first documentation in Homer's poems, the definition has been continually evolving (1). The clinical definition of sepsis remains challenging and ever changing as new criteria emerge (2). Sepsis, as a condition, exists on a spectrum of severity ranging from infection and bacteremia to sepsis and septic shock, which can eventually lead to multiple organ dysfunction syndrome (MODS) and death (3).

Over a 20-year span, research has revealed that many patients develop acute organ dysfunction in response to infection but without a measurable inflammatory excess (i.e., without the systemic inflammatory response syndrome [SIRS]). Improved definitions of sepsis have been proposed at international conferences which were held in 1991, 2001 and most recently in 2016 (Figure 1).

The 2016 SCCM/ESICM task force (The Society of Critical Care Medicine [SCCM] and the European Society of Intensive Care Medicine [ESICM]) defined sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection (4), while organ dysfunction was defined as an increase of two or more points in the Sequential organ failure assessment (SOFA) score (3).

Septic shock is defined as a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality (5). For clarity, the proposed criteria for septic shock, includes sepsis, plus the need for vasopressor therapy to elevate mean arterial pressure to ≥65 mmHg, with a serum lactate concentration >2.0 mmol/L after adequate fluid resuscitation (Figure 1). In addition to the drastic changes to the definitions, the task force recommended the elimination of the terms sepsis syndrome, septicemia, and severe sepsis (4).

The new sepsis definitions abandoned the SIRS criteria as the starting point for detecting sepsis, equated Sepsis-3 sepsis to Sepsis-2 severe sepsis and, for the first time, provided specific criteria for operationalizing the definitions (3,6). Severe sepsis and SIRS should therefore no longer be used since the latest (2016) sepsis and septic shock definitions include patients with evidence of tissue hypoperfusion and organ dysfunction (3).

Severe sepsis, which was associated with tissue hypoperfusion (i.e. elevated lactate, oliguria) or organ dysfunction (i.e. elevated creatinine, coagulopathy), is now referred to as sepsis (5,7).

SIRS is considered a clinical syndrome, that is characterized by dysregulated inflammation, defined as two or more abnormalities in temperature, heart rate, respiration, or white blood cell count (5).

Sepsis 1 (1991)[6]	**Sepsis 2 (2001)**[7]	**Sepsis 3 (2016)**[8]
Systemic inflammatory response syndrome (SIRS): systemic inflammatory response to a variety of severe clinical insults: Temperature >38°C or <36°C; heart rate > 90 beats per min; respiratory rate > 20 breaths per min or $PaCO_2$ < 32 mmHg; and white blood cell count > 12,000/cu mm, <4000/cu mm, or >10% immature (band) forms Sepsis is a systemic response to infection, manifested by two or more of the SIRS criteria as a result of infection. Severe sepsis: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension; hypoperfusion and perfusion abnormalities may include, but not limited to, lactic acidosis, oliguria, or an acute alteration in mental status Septic shock: Sepsis-induced, with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but not limited to, lactic acidosis, oliguria, or an acute alteration in mental status; patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.	Infection: Documented or suspected and some of the following: **General parameters:** Fever (core temperature > 38.3°C); hypothermia (core temperature < 36°C); heart rate > 90 beats per min or > 2 SD above the normal value for age; tachypnea: respiratory rate > 30 breaths per min; altered mental status; significant edema or positive fluid balance (>20 mL kg^{-1} over 24 h) Hyperglycemia (plasma glucose > 110 mg dL^{-1} or 7.7 mM L^{-1}) in the absence of diabetes **Inflammatory parameters:** Leukocytosis (white blood cell count > 12,000/μL); leukopenia (white blood cell count < 4000/μL); normal white blood cell count with > 10% immature forms; plasma C-reactive protein > 2 SD above the normal value; and plasma procalcitonin > 2 SD above the normal value **Hemodynamic parameters:** Arterial hypotension (systolic blood pressure < 90 mmHg, MAP < 70 mmHg, or a systolic blood pressure decrease > 40 mmHg in adults or < 2 SD below normal for age, mixed venous oxygen saturation > 70%, cardiac index > 3.5 L min^{-1} m^{-2}) Organ dysfunction parameters: Arterial hypoxemia (PaO_2/FIO_2 < 300); acute oliguria (urine output < 0.5 mL kg^{-1} h^{-1} or 45 mM L^{-1} for at least 2 h); creatinine increase ⩾ 0.5 mg dL^{-1}; coagulation abnormalities (international normalized ratio > 1.5 or activated partial thromboplastin time > 60 s); ileus (absent bowel sounds); thrombocytopenia (platelet count < 100,000 μL^{-1}) Hyperbilirubinemia (plasma total bilirubin > 4 mg dL^{-1} or 70 mmol L^{-1}) **Tissue perfusion parameters:** Hyperlactatemia (>3 mmol L^{-1}); decreased capillary refill or mottling	Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection. **Clinical criteria for sepsis:** Suspected or documented infection and an acute increase of ⩾2 SOFA points (Table 2) The task force considered that positive qSOFA (quick SOFA) criteria should also prompt consideration of possible infection in patients not previously recognized as infected. qSOFA criteria: Altered mental status (GCS score < 15); systolic blood pressure < 100 mmHg; respiratory rate > 22 breaths per min Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality. Septic shock can be identified with a clinical construct of sepsis with persisting hypotension, requiring vasopressor therapy to elevate MAP ⩾ 65 mm Hg and lactate > 2 mmol L^{-1} (18 mg dL^{-1}) despite adequate fluid resuscitation

FIO_2: fraction of inspired oxygen; GCS: Glasgow Coma Scale; MAP: mean arterial pressure; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; SOFA: sequential organ failure assessment.

Figure 1. Definitions of Sepsis
[Retrieved from Gyawali B. *et al.* (1)]

1.1.2. Epidemiology

Sepsis is one of the main causes of morbidity and mortality in critically ill patients, with an estimated 48.9 million (38.9–62.9) cases globally (8). Furthermore, it is considered the most preventable cause of death and disability in Europe (9). In a 2016 meta-analysis by Fleischmann *et al.*, the average population incidence rate of sepsis hospitalization in developed countries (the USA, Germany, Australia, New Zealand, Taiwan, Norway, Spain, and Sweden) was estimated at 270 per 100,000 person-years, with an in-hospital mortality rate of 26% (10).

Incidence is highest in the youngest and oldest age groups, with in-hospital mortality rising nearly linearly with age from age 40 onwards (11). In the developed world, hospitalization for sepsis is more common than hospitalizations for myocardial infarction and stroke combined (12,13). The frequency of septic shock was estimated at 10.4% (95% CI 5.9 to 16.1%) in studies reporting values for patients diagnosed at ICU admission. Amongst publications reporting values for patients diagnosed at any time during the ICU stay, the frequency was lower at 8.3% (95% CI 6.1 to 10.7%) (14).

Each year in Europe, more than 3.4 million individuals develop sepsis, 700,000 do not survive, while an additional one-third of survivors die during the following year. Many survivors face life-long consequences, such as new physical, mental, and cognitive problems.

Disability generated by sepsis is rarely emphasized, although recent European estimates suggest that approximately 2 million sepsis survivors will potentially suffer from long-term disabilities (9). The global epidemiological burden of sepsis is difficult to ascertain. It is estimated to affect more than 30 million people worldwide every year, possibly leading to 6 million deaths (15). The burden of sepsis is most likely highest in low- and middle-income countries (8).

Major differences between the new Sepsis-3 (16) and the old Sepsis-2 (5) definitions will contribute to alterations in sepsis and septic shock epidemiology (6). Despite the differences, Shankar-Hari *et al* showed in their 2017 study that Sepsis-2 severe sepsis and Sepsis-3 sepsis had similar incidence, mortality and showed significant risk-adjusted improvements in mortality over time (6).

A recent study of European ICU patients in which sepsis was defined according to the latest guidelines also suggested relative stability in the rate of sepsis (17). This may change with more studies, as the new definitions are adopted more broadly, but in the meantime, abandoning SIRS as the starting point for sepsis diagnoses does not seem to alter the incidence as most patients with organ dysfunction also tend also to have SIRS (6,14,18).

1.1.3. Mortality

Despite the use of modern antibiotics and resuscitation therapies, sepsis remains the tenth-most-common cause of death globally and the most common cause of death in patients with infections, especially when not detected within an adequate timeframe (19). It has been estimated that there were 11·0 million (95% UI 10·1–12·0) total sepsis-related deaths worldwide in 2017, representing 19·7% (18·2–21·4) of deaths that year (14).

In the US, sepsis is the most common cause of in-hospital deaths and costs more than US$24 billion annually (14,16). A recent literature review by Vincent *et al*., using data from the US, Europe and Canada reaffirmed the common occurrence of septic shock and reported a high mortality of around 38% (14).

Patients who die from sepsis can also be roughly divided in two groups; early and late deaths, within and after 72 hours of admission, respectively (20). In a study by Daviaud *et al.,* that included only patients suffering from septic shock, around 30% of deaths occurred swiftly, within 72 h of presentation. This group of patients already had severe organ dysfunction on presentation and died from fulminant multiple organ failure, the remainder died after a prolonged stay in the intensive care unit. (21).

Secondary complications, most notably nosocomial infections, are often the causes of late deaths in clinical practice along with elective withdrawal, due to a failure to recover. This is seen frequently on a background of significant underlying comorbidity, with limited physiological reserve (20).

Site of infection, organism, and the interaction between site and organism are strongly associated with survival from sepsis. To illustrate, urinary tract infections are rarely fatal regardless of microbial cause. Mortality from pulmonary sepsis varies widely by pathogen, from 13% for Streptococcus pneumoniae to 77% for Pseudomonas aeruginosa (21). Globally, for both sexes and all age groups combined, the most common underlying cause of sepsis-related death was lower respiratory infection in every year from 1990 to 2017 (14). A large metanalysis of 510 studies reported that gram-negative bacteremia was associated with a higher mortality compared with gram-positive bacteremia (16).

Overtime, outcomes in sepsis have improved overall, possibly due to a heightened focus on early diagnosis and progressive improvements in supportive care. Over the last few years, some European countries, such as Germany, have seen their sepsis-related mortality rate decrease (9). Unfortunately, in spite of all the developments in management, mortality rates still remain unacceptably high. In-hospital mortality rates in the USA are as high as 25–30% (14) , while correspondingly the rate in German hospitals is 24.3% (11).

Early detection is key for septic patient management, as prompt treatment leads to improved mortality and outcomes (4).

1.1.4. Etiology

The etiology is diverse but since sepsis is presumed to result from an underlying infection, it is therefore inherently an intermediate cause of health loss. The most common underlying cause of sepsis was diarrheal disease, in every year from 1990 to 2017, among all age groups, sexes and locations. Interestingly, this trend changes in 2017, with road traffic injury becoming the most common underlying cause of sepsis (14).

1.1.4.1. Risk factors

The many risk factors for sepsis are related to both the predisposition to develop an infection and the probability of developing acute organ dysfunction.

Common risk factors for increased risk of infection include chronic diseases (e.g., HIV infection, chronic obstructive pulmonary disease, diabetes, cancers) and immunosuppression (22). More than half of patients who develop sepsis also have at least one chronic health condition (16). It should be noted that various comorbidities increase the chance of developing sepsis, although not all increase the eventual risk of mortality, with diabetes as a notable example (23).

Risk factors for progression from infection to organ dysfunction are ill-defined, these may consist of established organ function, underlying health status and importantly the timing of treatment (20). Age, sex, ethnicity and socio-economic status all have impacts on the incidence of sepsis, highest at the extremes of age, in males and in Africans (20). The incidence of sepsis increases disproportionately in older demographics, with more than half of cases occurring in adults over 65 years of age (16). A recent study reported an inverse relationship between socioeconomic status and the risk of blood stream infection (24).

The differences in sepsis risk, by the various mentioned factors is not fully understood as genetic variances in susceptibility to infection are yet to be fully elucidated. Sorensen and associates (25) suggest, that genetic factors may be more important in outcomes of infectious diseases compared to cardiovascular disease (16). In this study, adopted children, whose biological parents died due to infectious causes, had a 5.8-fold increased risk of dying due to infections. In comparison, the increased risk of death due to cardiovascular causes was 4.5-fold, if their biological parents died of cardiovascular causes (25).

Interestingly, elevated body weight appears to have a controversial impact upon outcome, referred to as the 'obesity paradox' (26). Arabi *et al*. revealed that obesity may offer general protection against critical illness through increased energy reserves and/or the endocrine and paracrine properties of adipose tissue (20). On the contrary, accumulating evidence suggests that obese patients are more susceptible to infections and are more likely to develop serious complications to common infections (5).

In terms of environmental risk factors, sepsis is more common in colder months, both in the UK (35% higher in winter than in summer) (27) and US (17.7% higher in autumn than in summer) (20). The case fatality rate for sepsis is also higher in winter, despite similar severity of illness (16).

1.1.4.2. Microbiology

Sepsis can arise from both community-acquired and hospital-acquired infections. Of these infections, pneumonia, the most common manifestation, is associated with the highest mortality and accounts for about half of cases (28).

The next most common sites of infection are unspecified, followed by intraabdominal and subsequently, the genitourinary tract. Blood cultures are typically positive in only one-third of cases, while in many instances at all sites fail to yield positive results (16). An infectious organism is identified in about 60–65% of patients with sepsis and 75% of patients with ICU-acquired sepsis (20,29).

The type of organism causing sepsis is an important determinant of outcome. Although most recent studies have suggested an increasing incidence of gram-positive organisms, the latest European Prevalence of Infection in Intensive Care (EPIC II) study from 2007 reported more gram-negative organisms (62.2% vs. 46.8%) (30).

In recent years, gram-positive infections have been reported more often than gram-negative infections, although a 75-country point-prevalence study of 14,000 patients on intensive care units found that 62% of positive isolates were gram-negative bacteria, 47% were gram positive bacteria, 19% were fungi, while 18% of patients had multiple organisms identified (29).

Methicillin-sensitive Staphylococcus aureus, methicillin-resistant Staphylococcus aureus and Streptococcus pneumococcus are the most common gram-positive isolates. Escherichia coli, Pseudomonas species and Klebsiella species are the most common isolated gram negative, while fungal causes are predominantly caused by Candida species (20).

1.1.4.3. Pathobiology

Clinically, sepsis is diagnosed by the presence of acute infection and new onset organ dysfunction (31). The previously held notion of septicemia was of a non-specific term that described an individual who appeared unwell (presenting with SIRS) and had a proven bloodstream infection. The contemporary conceptualization of sepsis extends across pathogens (bacterial, fungal, viral, and parasitic), with the dysregulated host response as the core focus and most prominent source of morbidity and mortality (Figure 2). In recognition of the fact that numerous cases do not have confirmation, sepsis in the modern era of clinical medicine requires only that infection be suspected, rather than proven (1,20,31). This paradigm shift has occurred over the last decade due to the increasing knowledge base regarding sepsis pathophysiology and the growing relevance of non-inflammatory pathways (20).

At its core, sepsis is predominantly recognized as an acute inflammatory condition, mediated by a dysregulated activation of the innate immune system, triggered by infection (32). It is uncertain why immune responses that usually remain localized sometimes spread beyond the local environment causing sepsis (8). The cause is likely multifactorial and may include the direct effects of the invading microorganisms or their toxic products, release of large quantities of proinflammatory mediators and complement activation (Figure 2). In addition, some individuals may be genetically susceptible to developing sepsis (32).

1.1.5. Pathophysiology

Sepsis exists on a spectrum of severity from infection and bacteremia to sepsis and septic shock defined by life-threatening organ dysfunction caused by a dysregulated host response to infection (3).

It can be conceptualized as malignant intravascular inflammation (33). It is thought of as malignant, because it is uncontrolled, unregulated and self-sustaining. In sepsis, the blood spreads mediators that are usually confined to cell-to-cell interactions within the interstitial space, and is therefore considered an intravascular process. The host response is inflammatory in nature, as all characteristics of the septic response are exaggerations of the normal inflammatory response (31,33).

1.1.5.1. Host recognition and response

Pathogen-associated molecular patterns (PAMPs) are molecular components of invading pathogens (i.e. Lipopolysaccharide, peptidoglycan, bacterial DNA, etc.) that are recognized by host immune cell pathogen recognition receptors (PRRs) (34). Molecular components derived from damaged host cells contribute to stimulation of PRRs, known as danger-associated molecular patterns (DAMPs) or alarmins (20). Heat shock proteins, fibrinogen, hyaluronic acids and high-mobility group box-1 protein (HMGB-1) are examples of DAMPs that have been identified.

Four main PRR families have been recognized: Toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) and NOD-like receptors (NLRs) (20,34). PRR-mediated recognition is a vital defense mechanism of the host against invading pathogens, involving the initiation of innate immunity and upregulation of inflammatory gene expression (34,35). This triggers intracellular signaling cascades, leading to the activation of transcription factors. Most notably, NF-κβ, activator protein-1 and interferon regulatory factor (IRF) are key orchestrators of the innate induced immune response (32).

However, if the innate immune system is overwhelmed and fails to eradicate the pathogen, the growing bacterial load leads to the overstimulation of PRRs, which manifests in a dysregulated host response. The recognition of both the pathogen (PAMPs) and host damage (DAMPs) lead to perpetuating inflammation (Figure 2). PRR overstimulation, unlike regulated responses, does not benefit the host, but instead has deleterious effects including tissue injury, organ dysfunction and most notably the progression to and preservation of sepsis (20).

The transition to sepsis occurs when the release of proinflammatory mediators in response to an infection surpasses the limits of the local environment, leading to a more systemic response (31).

1.1.5.2. Hyperinflammation and the complement system

Target genes of PRR stimulation code for proinflammatory cytokines, such as tumor necrosis factor TNF, IL-1β, IL-12 and IL-18 (31). The regulation of the host response exists in a delicate equilibrium between PRR overstimulation and several mechanisms dampening the transcription of proinflammatory cytokines, namely negative regulators MyD88, single-immunoglobulin interleukin IL-1 receptor-related molecule (SIGIRR), toll-interacting protein (TOLLIP) and suppressor of cytokine signaling (SOCS) (1,36).

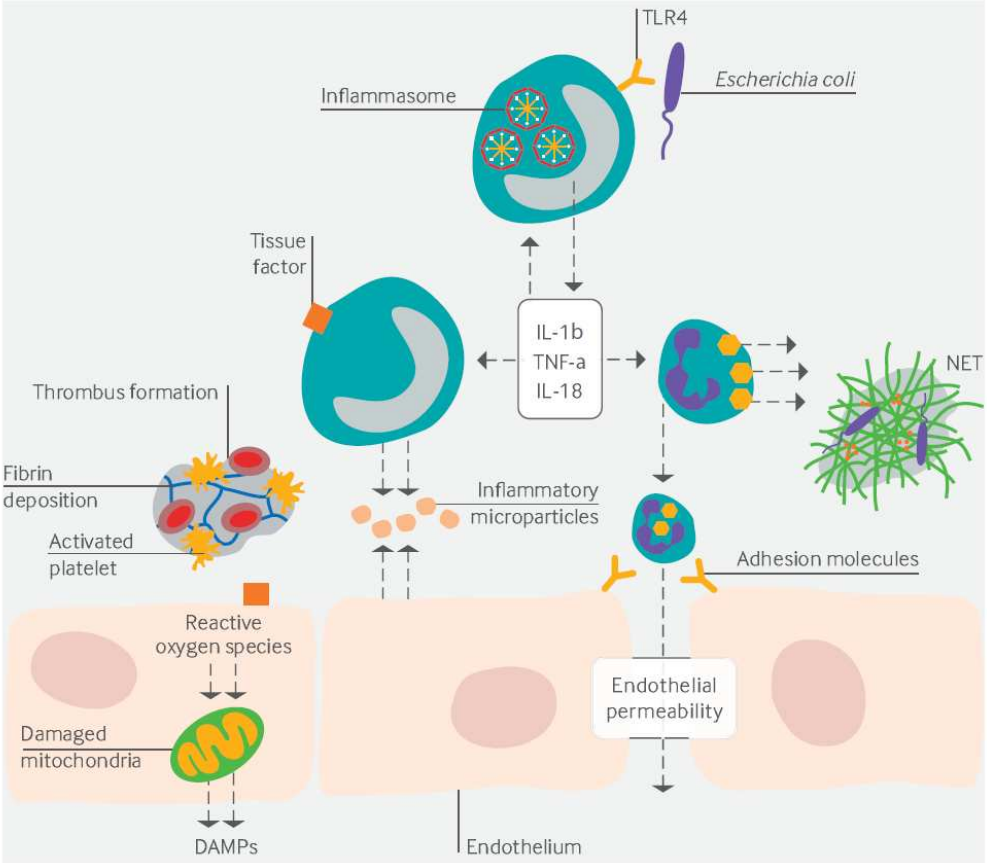

Figure 2. Self-reinforcing pathophysiological processes in sepsis.
Endothelial injury results in the activation of monocytes and granulocytes, endothelial barrier breakdown, immunothrombosis and DIC. DAMPs - damage associated molecular patterns, IL - interleukin, TLR4 -Toll-like receptor 4, TNF-a- tumor necrosis factor alpha
[Retrieved from Gotts *et al.* (36)]

The classic pleiotropic hyperinflammatory response of sepsis ensues when this balance is disturbed. This includes activation of the complement and coagulation systems and disturbance of vascular permeability, (20) all factors which are considered highly significant in sepsis mortality (Figure 2). An effective collaboration between the complement system and proinflammatory mediators is crucial for efficient tagging and phagocytosis of pathogens. Disturbance of these defensive processes outlines the dysregulated host response seen in sepsis (Figure 2).

Several experimental sepsis studies have highlighted the beneficial effect of blockage of C5a signaling on outcome, (37) leading to the consideration for a potential therapeutic target in sepsis (20). Neutrophil dysfunction, apoptosis of lymphoid cells, exacerbation of systemic inflammation, cardiomyopathy, disseminated intravascular coagulation (DIC) and complications related with multiple organ failure have all been associated with deleterious effects of C5a in sepsis (38).

1.1.5.3. Systemic Effects

1.1.5.3.1. Endothelial dysfunction and coagulation dysregulation

The endothelium plays vital roles in the regulation of vasomotor tone, movement of cellular nutrients, the coagulation system and the maintenance of dynamic equilibrium of both inflammatory and anti-inflammatory signaling (36).

Sepsis induces profound alterations to endothelium physiology, including increased leukocyte adhesion, a shift to a procoagulant state, vasodilation and the loss of barrier function. All factors manifest in excess barrier leakage and widespread tissue edema (39). Disturbances in microcirculation primarily develop as a result of impaired responses to local stimulation in combination with obstruction of microvasculature, by microthrombi and plugs of blood cells (36,40). The activation of PRRs leads to upregulation of inflammatory mediators, which results in a systemic inflammatory response, including activation of the coagulation system and concurrent downregulation of anticoagulant mechanisms (41). Coagulation abnormalities can range from mild to clinically relevant fulminant coagulopathies, namely disseminated intravascular coagulation (DIC).

The most severe syndrome of disrupted hemostasis, DIC, is associated with increased organ dysfunction, hemorrhage (owing to consumption of platelets and clotting factors) and mortality (20). It is manifest due to widespread tissue factor expression, fibrin deposition and impaired anticoagulation mechanisms (including activated protein C) (Figure 2) (36).

The endothelial changes in sepsis are associated with alterations in barrier function of organ systems (15). The loss of both endothelial and epithelial barrier integrity is a key mechanism of widespread lethal organ dysfunction. This increased permeability sets in motion a vicious cycle of bacterial translocation, tissue injury by extravasated substances and worsening systemic inflammation, that can perpetuate multiple organ dysfunction. (36).

1.1.5.3.2. Immune system dysfunction

The immune system in sepsis is incapable of initiating an adequate and effective immune response to secondary bacterial, viral, or fungal infections (1). In many patients, immune suppression can already be detected on admission to the ICU and is a major feature in those patients, that remain in the ICU for extended periods of time (7,42). Targeted immune-enhancing therapy has shown to be beneficial for selected patients with immune suppression (7,42).

Sepsis-induced immune suppression is characterized by massive apoptosis and thus a depletion of immune cells, reprogramming of monocytes and macrophages to a state of decreased capacity to release proinflammatory cytokines and a disturbed metabolic equilibrium (20). Inhibition of lymphocyte apoptosis was associated with improved outcomes in various experimental sepsis models, suggesting a causal relationship between lymphocyte apoptosis and sepsis mortality (7,42).

In other studies of septic patients, neutrophils were found to have expressed fewer chemokine receptors and diminished chemotaxis in response to IL-8. Biemond *et al.* and Hotchkiss *et al.* have also demonstrated decreased production of crucial cytokines, such as IL-6 and TNF in response to endotoxin (1). Spleens harvested from deceased septic ICU patients were largely depleted of CD4+ and CD8+ T cells. The loss of CD4 + T cells seems to be the result of widespread apoptosis, which severely hinders the capability of mounting an appropriately formidable immune response to superimposed infections (35,36).

The early proinflammatory state in sepsis often develops into a prolonged state of immune system dysfunction (36). Studies show low lymphocyte counts early in sepsis (specifically day 4 of diagnosis) to be predictive of both 28-day and 1-year mortality. Furthermore, this implies that early lymphopenia can serve as a bio-marker of immunosuppression in sepsis (1).

During the course of the illness, reactivation of multiple viruses, including cytomegalovirus, Epstein-Barr virus, herpes simplex virus and human herpesvirus 6 can be seen. Therefore, it can be concluded that in protracted sepsis there is a microbiologic tendency towards subsequent infection with less virulent organisms (36).

1.1.5.4. Organ-specific effects

A dysregulated host response to infection leads to organ dysfunction due to disturbed inflammatory homeostasis and immune system performance.

The progression of sepsis through release of endogenous molecules by injured cells (DAMPs or alarmins), pathogen virulence and load (PAMPs), is augmented by the host recognition response (Figure 3)(20).

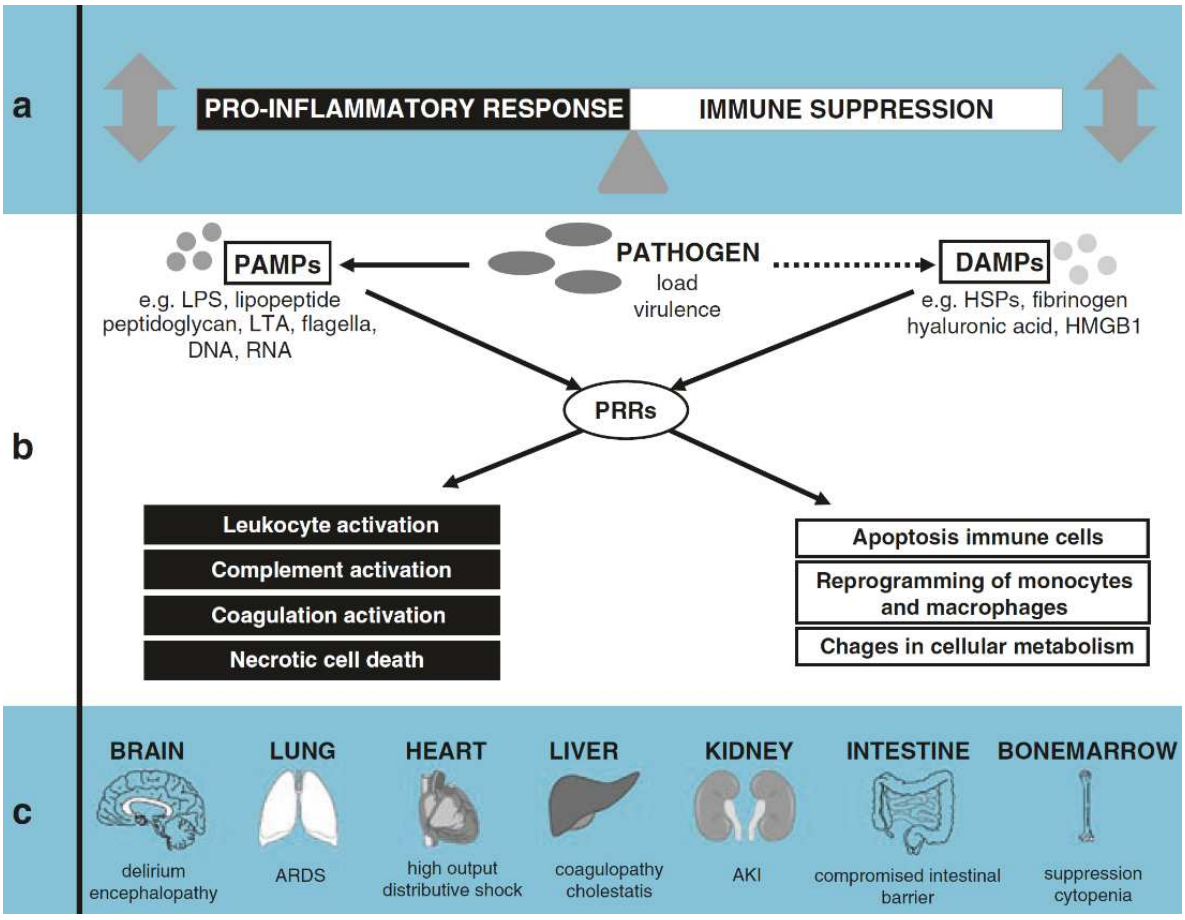

Figure. 3. Pathogenesis of sepsis.
(a)Dysregulated host response to infection: disturbed inflammatory balance results in, hyperinflammation and immune suppression *(b) Vicious progression cycle:* PRRs identify PAMPs and DAMPs leading to proinflammatory and immune suppressive consequences
(c) Sepsis is by definition a disease with respective criteria for organ failure.
[Retrieved from Trivedi et al. (20)]

1.1.5.4.1. Circulation

In sepsis, the most severe expression of circulatory dysfunction is hypotension due to diffuse uncontrolled vasodilation. It has been proposed, that this is the result of dysregulated metabolic autoregulation by vasoactive mediators, such as nitric oxide (NO) and prostacyclin (43).

Landry *et al.* found impaired compensatory production of antidiuretic hormone (vasopressin) to be present in patients with septic shock compared with those in cardiogenic shock (3.1 versus 22.7 pg/mL, respectively), even though both groups recorded similar systemic blood pressures (44). This may play a role in influencing the degree of vasodilation and loss of effective circulating volume seen in sepsis. In addition, numerous other studies have demonstrated the utilization of vasopressin to improve hemodynamics, while simultaneously allowing withdrawal of other vasopressors (45,46).

Hypotension in sepsis is also a consequence of intravascular fluid redistribution. Increased capillary pressure leading to leakage is caused by a combination of reduced arterial vascular tone and increasingly more permeable endothelium (31).

The central circulation (i.e. heart and large vessels) is affected early on in sepsis, with released myocardial depressant substances, causing reduced systolic and diastolic function (31,47). In the presence of systemic vasodilation and decreased effective circulating volume, it is essential that the Frank-Starling mechanism succeeds in preserving ventricular performance. Those with pre-existing cardiac disease (i.e. previous infarction, coronary artery disease, etc.) are often incapable of increasing their cardiac output to an appropriate extent.

Vascular hypo-responsiveness is the primary disturbance affecting regional circulation (i.e. small vessels leading to and within the organs). The inability to appropriately vasoconstrict leads to a failure of adequate distribution and maintenance of effective systemic blood flow to organ systems. This crucial function is dysregulated in sepsis in comparison to when oxygen delivery is depressed in normal physiological states, which leads compensatory redistribution of blood flow from splanchnic organs to vital organs (heart and brain) (31).

The microcirculation (i.e. capillaries) is considered the most important target in sepsis as it is associated with a reduction in the number of functional capillaries, which results in decrease capacity to effectively extract oxygen (48). In a study using reflectance spectrophotometry and orthogonal polarization spectral imaging, in vivo visualization of the sublingual and gastric microvasculature revealed, that patients with severe sepsis have reduced capillary density compared to normal controls or critically ill patients without sepsis (49). This may be explained by the extrinsic compression of capillary beds by tissue edema and endothelial swelling, that take place in a state of sepsis.

Lastly, it should be noted that the loss of cellular deformability amongst cell lines, namely leukocytes and erythrocytes, leads to stasis in capillaries (31).

1.1.5.4.2. The lungs

Injury to pulmonary vasculature during sepsis causes a disruption of capillary blood flow and augmented microvascular permeability, leading to both interstitial and alveolar pulmonary edema (50,51). Immune cell infiltration proceeds, characterized by neutrophil entrapment within the lung's microcirculation. This initiates and reinforces the progressive amplification of the alveolocapillary membrane injury.

Recurrent insults lead to the development of pulmonary edema, producing ventilation-perfusion mismatch, eventually causing the development of hypoxemia. Acute respiratory distress syndrome is a manifestation of these effects and is a prominent feature of sepsis pathophysiology (31).

1.1.5.4.3. The gastrointestinal tract

The typical circulatory abnormalities found in sepsis have been shown to weaken the gastrointestinal barrier function, permitting predominantly lymphatic rather than portal vein translocation of bacteria and endotoxins into the systemic circulation, extending the septic response (50–52).

Doig *et al.* found supporting evidence in a prospective cohort that showed increased intestinal permeability is predictive of the development of multiple organ dysfunction syndrome. This was also successfully demonstrated in animal models of sepsis (53).

Changes in diversity and composition of the intestinal microbiome have been found to have negative effects regarding morbidity and mortality in septic patients. Recent evidence suggests a complex and vital relationship between gut flora and the mediation of sepsis pathology (54).

1.1.5.4.4. The hepatobiliary system

The first line of defense regarding pathogens in the portal system is the reticuloendothelial system of the liver playing an important role in the elimination of bacteria and bacterial-derived products.

Normally, bacteria that have entered through the gastrointestinal tract can be cleared, but liver dysfunction prevents the elimination of enteric-derived endotoxins and other products. Sepsis induced hepatocyte dysfunction impairs efficient pattern recognition (via reticuloendothelial system), resulting in an inadequate localized cytokine response, while simultaneously allowing for direct spillover of potentially harmful products into the systemic circulation (50,51).

Sepsis has detrimental effects on many critical hepatic functions, which also includes the clearance of bilirubin. Cholestasis, as well as the transport and processing of enteric pathogen lipids (55) are impaired, which together augment stimulation of systemic inflammation (36).

1.1.5.4.5. The kidney

Sepsis is often accompanied by renal failure, with acute kidney injury (AKI) substantially increasing the risk of death (31,56). The processes, by which endotoxins in sepsis lead to AKI, are yet to be fully understood.

Acute tubular necrosis induced by reduced renal perfusion and/or hypoxemia is one of the key mechanisms (50,51). Although in the past, septic AKI has been attributed to renal hypoperfusion and acute tubular necrosis, growing evidence suggest that septic acute renal failure is only partially sustained by renal hypoperfusion (56).

The effects of systemic hypotension, direct renal vasoconstriction, release of cytokines (i.e. tumor necrosis factor [TNF]) and activation of neutrophils by endotoxin and FMLP (a chemotactic peptide in bacterial cell walls) may have roles in the development of renal injury. Septic AKI seems to involve more complex and subtle mechanisms of cytokine and immune mediated microvascular and tubular dysfunction (36)

1.1.5.4.6. Nervous system

Early onset encephalopathy is a common clinical finding in severe sepsis, often occurring before the failure of other organs. The neurological derangement exists on a continuum from mildly impaired attention to deep coma (57).

Delirium, as assessed by the confusion assessment method (CAM-ICU method) is independently related with mortality, enduring neurocognitive deficits and very common in ventilated patients (58). Dysfunction of the central nervous system (CNS) can be caused directly by infectious processes, although more frequently, infections set in motion a series of aseptic events that disturb neurologic function.

Systemic endothelial dysfunction has been found to compromise the selectivity of blood-brain barrier (BBB) permeability, leading to excessive infiltration of inflammatory cells and cytokines into the CNS (36). Cytokines are actively transported across the BBB in these conditions, which allows for the exposure to toxic mediators. The result is perivascular edema, oxidative stress, leukoencephalopathy and diffuse neurotransmitter abnormalities (59).

Dysfunction of the CNS has also been attributed to alterations in neuronal cell metabolism and cell signaling, due to effects of inflammatory mediators, which is only perpetuated by the loss of BBB integrity (59).

Both hepatic and renal dysfunction intensify the influx of harmful metabolic products into the CNS. The addition of coagulopathy and impaired autoregulation of cerebral blood flow can produce diffuse areas of ischemia and hemorrhage (60).

There is growing recognition that the parasympathetic nervous system may be an active mediator in the early development of systemic inflammation in sepsis. Cholinergic stimulation inducing an anti-inflammatory effect has been demonstrated in numerous animal models. Afferent vagus nerve stimulation during sepsis increases the secretion of corticotropin-releasing hormone (CRH), adrenocorticotropin hormone (ACTH), and cortisol through cholinergic efferents. This in turn inhibits inflammatory cytokine production by innate immune cells in the spleen and gut, producing the anti-inflammatory effect (61). Evidence of this was demonstrated in studies where cortisol secretion was suppressed by subdiaphragmatic vagotomy (31). External vagal nerve stimulation was found to diminish cytokine signaling and endothelial injury in animal models of sepsis as well as shock from ischemia-reperfusion, burns, and pancreatitis (36,62). In addition, acetylcholine receptor agonists have been found to reduce the dysregulated response to sepsis (63).

1.1.5.5. Self-reinforcement of septic organ dysfunction

Septic organ dysfunction often perpetuates critical illness in a self-reinforcing manner through several well-defined pathways that manifest as 'chronic critical illness'(64) .
Features of septic critical illness and treatment reinforcement are the following:

1. ARDS (65)
    - Often requires mechanical ventilation for respiratory support
        - Ventilation further injures the lungs and enhances systemic inflammation
2. Sedatives (66)
    - Needed to compel compliance with positive pressure ventilation
        - worsen septic associated encephalopathy and delirium,
        - lead to reduced mobility
        - augment catabolism
        - induce severe neuromuscular weakness
3. Intestinal barrier dysfunction (53)
        - ongoing systemic translocation of pathogenic organisms
        - impaired nutritional status

4. Immune system dysfunction (36)
    - high susceptibility to new infections
    - patients commonly treated with broad spectrum antibiotics (potential development of resistant pathogens)
    - propensity for resistant bacteria and opportunistic organisms.
    - patients have portals for nosocomial infections (endotracheal tube, intravascular, bladder catheters)

The combined effects of these self-reinforcing processes explains a large extent of the morbidity of severe sepsis, notably the tendency to develop what has been termed "chronic critical illness" (64). It has led to the increased emphasis on meticulous, evidenced based supportive critical care, which has probably helped improve outcomes in sepsis (36).

1.1.5.6. Diagnosis and clinical presentation

Correctly recognizing a septic patient can be difficult, even for the experienced doctor. Presentation may be variable and in the early stages present with non-specific symptoms. Features of sepsis may be confounded by pre-existing comorbidities and organ dysfunction may not be immediately apparent. Deterioration may be gradual over days or abrupt and severe over just a few hours. This emphasizes the importance of accurate, easy-to-use criteria for sepsis and its components, infection and organ dysfunction.

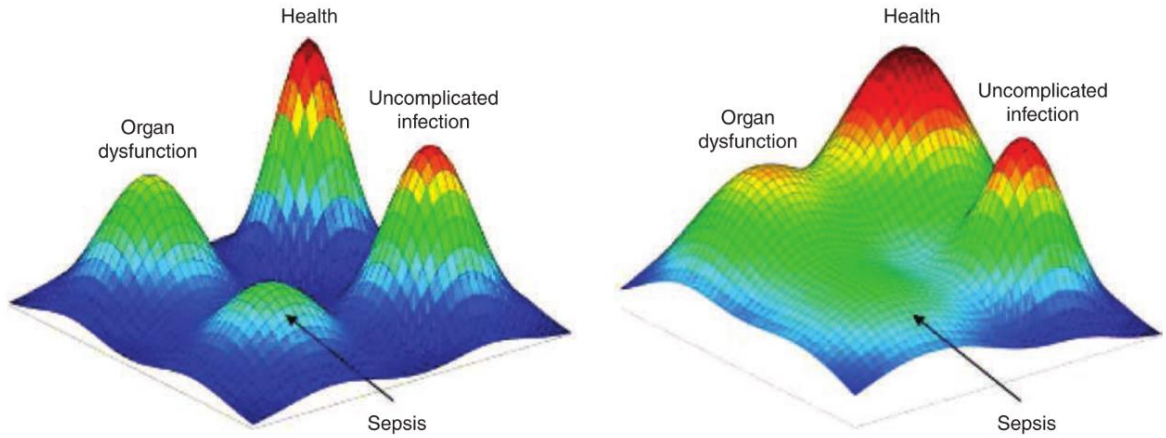

Figure 4. The "zone of rarity" problem in sepsis
Schematic of ideal and typical distributions of surface phenomena (clinical and biologic features) among patients with and without disease. (left – Ideal case, Right – In reality)
[Adapted from DC Angus *et al*. (67)]

In the ideal scenario, criteria clearly distinguish sepsis patients from other patients with uncomplicated infection or organ dysfunction, as illustrated in Figure 4 (*left*). However, the reality is, existing criteria fail to make clear distinctions, leaving a significant proportion of patients in areas of uncertainty (Figure 4, *right*). Distinct "zones of rarity' between patient groups allow for accurate detection and stratification by applied criteria (67).

Patients are initially treated empirically for sepsis, but in 20 to 25% of cases, a sepsis mimic is belatedly identified. Many mimics exist, ranging from pulmonary embolus and heart failure to beriberi, pheochromocytoma, hemophagocytic syndrome and various autoimmune diseases such as systemic lupus erythematosus (20).

1.1.6. Markers

There is no specific test for sepsis, nor is there a gold-standard method for determining whether a patient is septic. Biomarkers have been evaluated for several applications in patients with sepsis including diagnosis of infection, prognostication and therapeutic guidance. Currently available biomarkers are not specific for sepsis and are raised in other inflammatory processes, making them more useful to rule out than to rule in a diagnosis of infection (20) (Figure 5).

Typically, patients with sepsis can be treated efficiently with early intravascular fluid and antibiotics in the ICU to decreased mortality. However, it is difficult to decide early on whether to apply these methods, due to the existence of non-infectious systemic inflammatory response syndrome (SIRS) (68). Therefore, identifying a biomarker that can efficiently distinguish sepsis from non-infectious SIRS is of great importance (69). More than 170 biomarkers have been studied for potential use in septic patients (20). Recent studies have focused their investigations on candidate biomarkers to detect sepsis, such as procalcitonin (PCT), C-reactive protein (CRP), lipopolysaccharide-binding protein (LBP), interleukins, provasopressin and myeloid cells expressing triggering receptor-1 (TREM-1) (69). However, none of them have been proven to be accurate enough to distinguish sepsis from SIRS.

The Surviving Sepsis Campaign 'weakly' recommended the measurement of procalcitonin levels to support shortening the duration or discontinuation of antimicrobial therapy in sepsis patients under low quality of evidence (7). The guidelines for the management of sepsis mention that sepsis biomarkers can complement clinical evaluation (7), but in the Sepsis-3 definition consensus, the role of biomarkers in sepsis diagnosis remains undefined (15,70).

None of the individual markers regularly utilized, even at their highest expected value, have the capability to ascertain 100 % sensitivity and specificity, regarding the occurrence of sepsis in a patient with SIRS. Although some have potential to be truly useful and can be rationally implemented in routine practice. An obvious suggestion proposed by various authors, is to establish a set combinations of a few markers with the purpose of defining a better and perhaps ideal diagnosis tool (71).

It should be emphasized, that all biomarker values need to be interpreted in the context of a full clinical history, examination and the presence of other signs and symptoms of infection (Figure 5). This aspect is true for all potential biomarker roles. The specific biomarkers discussed in this dissertation are those relevant to the study conducted, namely lactate, CRP and procalcitonin.

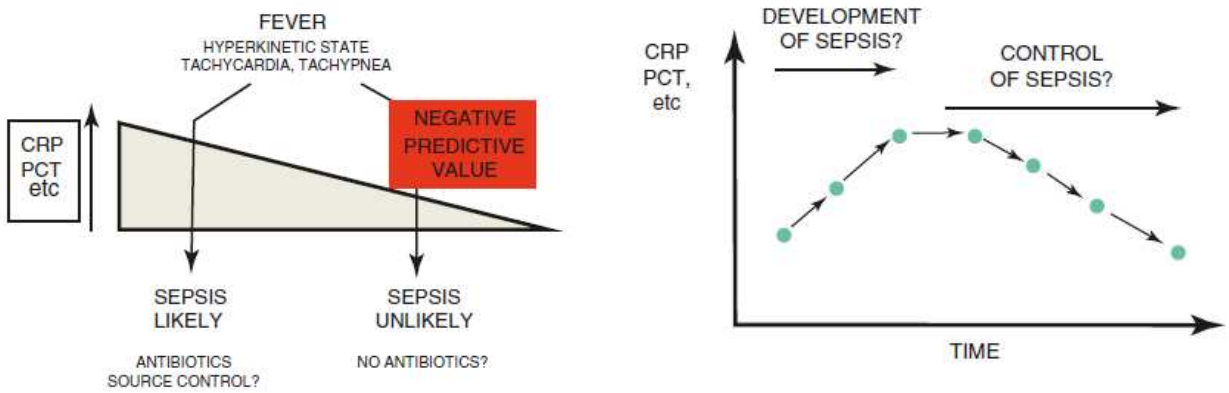

Figure 5. Biomarkers in sepsis: *(Left)* Biomarkers are more useful to rule out than rule in infection. *(Right)* Biomarker concentrations increase as sepsis develops, but decrease as sepsis resolves with effective treatment.
[Adapted from Trivedi *et al*. (20)]

1.1.6.1. Lactate

Serum lactate levels are a sensitive but nonspecific indicator of metabolic stress (72). Converted from pyruvate, a product of anaerobic glycolysis, lactate is increased during hypoxia, stress and many critical illnesses (73). In septic patients with multiple organ failure, it has been reported, that lactate is secreted from the most severely affected organs. Lactate is released at the sites of infection and inflammation and is considered to be related to amplified glycolysis in recruited and activated leukocytes at the sites of infection (72). Both an increased production and a decreased clearance can lead to heightened levels of circulating lactate in patients (71).

Research has regularly demonstrated the positive association between higher levels of lactate and increased mortality (74). Lactate levels are inversely proportional to outcome (19), while its early clearance is associated with improved status (75). In a substantial amount of cases, lactate levels, particularly associated with poor clearance, were a predictor of mortality. High lactate levels have also been regularly described in any SIRS patients such as those with burns, post-trauma and post-surgically (71).

Different lactate thresholds have been recommended in various studies as an early aggressive resuscitation predictor (19). Based on this, early identification of elevated serum lactate levels can potentially lead to early identification of patients, who are in danger of poor outcomes.

1.1.6.2. C-Reactive Protein (CRP)

C-reactive protein is an acute-phase protein first described by Tillett and Francis in 1930 (76). It is synthesized predominantly by hepatocytes in response to cytokine stimulation, notably interleukin IL-6. Elevated CRP concentrations are used in nearly all areas of medicine as a general indicator of inflammation, to follow disease status and response to treatment in various conditions (32). Therefore, it generally lacks specificity for diagnosis of sepsis. Nevertheless, CRP is a sensitive marker to distinguish sepsis from non-septic causes of inflammation in the early onset of diseases and generally in ICUs (77). Its wide applicability, in terms of measuring disease status, the low cost and the fact that it is readily available make it a important parameter in medical practice.

C-reactive protein has a half-life of approximately 19 h, and levels begin to rise after 12 to 24 h, peaking within 2 to 3 days (20). It is present in a homeostatic state, with levels <47.61 nmol/L (<5 mg/L). Rises above the norm can increase concentrations1000 fold within 24 to 48 h (32), reaching levels in excess of 4762 nmol/L (500 mg/L) during inflammation. Numerous studies have reported significantly higher levels of CRP in sepsis patients as compared to critically ill adult patients with SIRS, independent of the clinical score (71,78). Although not specific itself, the combination of CRP and raised temperature increases the specificity for infection diagnosis to 100 % among critically ill patients (19,79).

Some studies reported significant higher mean CRP levels for bacterial sepsis, especially for discrimination of gram-negative bacterial from fungal causes of sepsis (80,81). Although CRP levels are commonly elevated in bacterial etiologies of sepsis, one study showed that a cut-off above 59.3 mg/L for CRP could discriminate gram-negative from gram-positive bacterial sepsis (32).

In terms of prognosis, Tschaikowsky *et al.* demonstrated that in regards to post-operative sepsis, on day 7, concentration of CRP has greater prognostic value than many other frequently used parameters and scoring systems (i.e. APACHE II score) (82). CRP levels can also be a useful tool to monitor the efficiency of initial antimicrobial therapy: CRP levels decreased more rapidly and to a greater degree in sepsis patients with a favorable response to initial antibiotics. In contrast, an increase in CRP of at least 209.5 nmol/L (22 mg/L) in the first 48h was associated with ineffective initial treatment (71).

Several meta-analyses have illustrated that the usefulness of CRP depends on the type of patients for whom an infection is suspected (83). Depending on the studies, the sensitivity of CRP varies from 30 to 97.2 % and its specificity from 67 to 100 % in adult and pediatric sepsis patients (71).

1.1.6.3. Procalcitonin (PCT)

Procalcitonin, an acute-phase protein, is a prohormone of calcitonin and is primarily expressed in the C-cells of the thyroid gland under physiological conditions and is rarely detectable in healthy individuals (32). In the setting of sepsis, PCT is produced by multiple tissues, namely hepatocytes and adipocytes, in response to inflammatory cytokines and bacterial endotoxins, resulting in increased circulating concentrations (20). Production is triggered by direct or indirect mechanisms, directly by endotoxin (component of the cell wall from gram-negative bacteria) or indirectly through the induction of proinflammatory cytokines, including TNF-α and IL-6 (84). PCT levels begin to rise within 3–4 h and peak within 6–24 h, earlier than CRP (85), with a half-life of approximately 22 to 33h in the serum. Half-life may be markedly prolonged in patients with renal dysfunction (68).

In terms of specificity, PCT concentrations are increased in other inflammatory conditions, such as pancreatitis or after polytrauma or major surgery. Levels during systemic bacterial infections are typically higher than in these non-infectious inflammatory states (20). Several studies also demonstrated superior diagnostic accuracy of PCT for sepsis, compared to other markers and additionally revealed that PCT is a mediator of the deleterious effects of systemic infection. Over the last decade, PCT has received extensive interest as a potential marker of infection to assess the presence, clearance and eradication of infection; predict mortality; and guide antibiotic management (86). A meta-analysis by Wacker *et al.* showed that elevated levels of PCT can be useful in the early diagnosis of sepsis (87).

Moreover, PCT is considered to be valuable in optimizing antibiotic therapy. A recent analysis assessing the efficacy of PCT-guided antibiotic treatment regimens demonstrated that safe discontinuation of antibiotics significantly shortens antibiotic exposure in critically ill patients (88). Although PCT-guided therapy may be associated with reduced antibiotic exposure, there is no consensus on cut-off points at which antibiotics could be safely stopped or on which algorithm, of the many that have been tested, is most effective. Such decisions must be made at an individual patient level.

Numerous studies have assessed the potential role of PCT in predicting etiology of sepsis, with a few reporting higher levels of PCT in gram-negative bacterial sepsis compared with gram-positive bacterial sepsis (81,89,90). Additionally, studies demonstrated discriminating higher levels of PCT in sepsis with bacterial cause compared with fungal cause, as PCT levels in fungal sepsis are relatively low (32,80,81,89).

It should be pointed out that most studies showed no or only moderate ability to distinguish between gram-positive bacterial and fungal infections (32,80,81). It has been suggested that PCT secretion can be directly induced by endotoxins (LPS), which is exclusively secreted by gram-negative bacteria, by LPS activation of TLR-4 signaling pathways. In contrast, gram-positive bacteria mainly activate TLR-2 signaling pathways, therefore manifesting in a different immune response (32).

Thomas-Rüddel *et al.* (89) showed that PCT significantly differs between pathogen species, with highest concentrations measured in patients with Escherichia coli and other Enterobacteriaceae infections, both of which are common gram-negative bacteria. An explanation for this variation, could be that PCT elevation depends on not only specific organisms but also the location of infection, as highest PCT values have been observed in urogenital and abdominal infections (20).

A subgroup analysis performed by Leng *et al.* (90) on different sites of infections, confirmed that high concentrations of PCT could distinguish between gram-negative from gram-positive bacterial infections, especially in abdominal urogenital infections and lower respiratory tract infections (32).

1.1.6.3.4. Cut-off values for sepsis biomarkers

Changing the cut-off means altering the sensitivity of a test at the cost of specificity or vice versa. False-negative results lead to the absence of appropriate treatment, which can have fatal outcomes in patients with sepsis (91). To avert antibiotic resistance, increased costs and side-effects, critically ill patients without bacterial infections, must be identified accordingly. Furthermore, a rational threshold is required, as the most substantial feature of a biomarker is its potential to change clinical decision making.

Generally, blood lactate concentration of > 2 mmol/L is considered a nonspecific marker of cellular hypoxia from hypoperfusion, that is commonly found in sepsis (20). Moreover, the International Consensus for Sepsis and Septic shock (Sepsis-3) defined septic shock by incorporating a serum lactate level > 2 mmol/L (15).

An optimal cut-off value of CRP for the diagnosis of sepsis has yet to be established, but various studies suggest that 50–100 mg/L may be sensible (68). However, a single CRP measurement often may not be important for the diagnosis of sepsis, since CRP is a quite unspecific parameter. This is particularly evident in critically ill patients, as elevations may be due to various etiologies without sepsis (83). Due to the extended clinical half-life, serial CRP measurements provide only a limited information in critically ill patients (68).

The cut-off for procalcitonin concentration between numerous studies varies significantly (median 1·1 ng/mL, IQR 0·5–2·0). The absence of a clinical threshold effect suggests that a cut-off between 1·0 and 2·0 ng/mL is useful in the detection of patients with sepsis and distinction from other inflammatory conditions (91).

1.1.7. Tools for the detection of sepsis/septic shock

Scoring systems are tools that may heighten the clinical suspicion for sepsis and encourage physicians to perform time-critical interventions. A key strategy for improving sepsis management is to identify the subgroup of patients with infection who are at high risk of adverse outcomes. This may aid clinical decision making for timely treatment, such as administration of life-saving antibiotics (92).

The Surviving Sepsis Campaign recommends the use of sepsis screening, which has been shown to reduce treatment time and improve outcomes (7). The current path to optimal treatment involves early detection, whether in the emergency department or an intensive care setting. With this in mind, it would stand that the most sensitive and specific stratification scores should be applied to enhance the accuracy of detective capabilities. Importantly, scoring systems employed must have a low enough threshold to minimize missed sepsis cases (93).

Several risk stratification scores have been devised both for detection and prognostication of sepsis. These include Systemic Inflammatory Response Syndrome (SIRS) (Figure 7), SOFA, Quick Sequential Organ Failure Assessment (qSOFA) (Figure 8) and most recently, National Early Warning Score 2 (NEWS2) (Figure 9) (94). Current risk stratification scores used for bedside detection of sepsis, as outlined by the third international consensus (sepsis-3), are Quick Sequential Organ Failure Assessment (qSOFA) and the SOFA (93).

1.1.7.1. Intended setting and implementation

The initial intended hospital locations and uses for each respective scoring system varies. SIRS is the only criteria initially intended for diagnostic purposes, while SOFA for is intended for prognosis and qSOFA for screening (Figure 6). NEWS2 is the only set of criteria not primarily intended for a septic patient population, but rather a clinical evaluation of acute deterioration.

Dectection Tools	Location	Population	Intended Use	SS/SS AUROC	Age	Heart Rate	Respiratory Rate	Temperature	Blood Pressure	O2 Sat./Supp. O2/FiO2	Mental Status	Medical History	CBC/Differential	Basic Metabolic Panel	Liver Function Tests	Urine Output	Arterial Blood Gas	Other Late Variables
SIRS	Non-ICU	Sepsis	Diagnosis	**0.88**		✔	O	✔					✔				O	
qSOFA	Non-ICU	Sepsis	Screening	**0.81**			✔		✔		✔							
NEWS2	Inpatient	All	Deterioration	**0.91**		✔	✔	✔	✔	✔	✔							
MEDS	ED	Sepsis	Prognosis	-	✔	✔	✔	O	O	O	✔	✔	✔					✔
SOFA	ICU	Sepsis	Prognosis	-					✔	✔	✔		✔	O	✔	O	O	
MODS	ICU	All	Prognosis	-		✔			✔	✔	✔		✔	✔	✔		✔	✔
APACHE II	ICU	All	Prognosis	-	✔	✔	✔	✔	✔		✔	✔	✔	✔		O	✔	
SAPS II	ICU	All	Prognosis	-		✔		✔	✔	✔	✔			✔	✔	✔	✔	

✔ = Required
O = Optional/alternative
= Not available at triage

--- Increasing Clinical Time --->

Figure 6. Scoring systems' Characteristics and Variables
SIRS - Systemic Inflammatory Response Syndrome), qSOFA - Quick Sequential Organ Failure Assessment, NEWS2 - National Early Warning Score 2, MEDS - Mortality in Emergency Department Sepsis, SOFA – Sequential Organ Failure Assessment, MODS – Multiple Organ Dysfunction Score, APACHE II – Acute Physiology and Chronic Health Evaluation II, SAPS II – Simplified Acute Physiology Score II, SS/SS – Severe sepsis/Septic shock, AUROC – Area Under Receiver Operator Curve
[Adapted from Usman *et al.* (93)]

NEWS2 and qSOFA do not diagnose infection; they merely identify patients with a high risk of adverse outcomes (92). Despite the differing initial aims of these scoring systems, all may be used by clinicians to evaluate illness severity and prognosis in patients with suspected infection or sepsis (Figure 6).

Such scores can offer prognostication and enable the trajectory of illness to be determined; however, they should complement, rather than replace sound clinical judgment. It is therefore important to determine their relative accuracy in achieving these goals.

1.1.7.2. Systemic Inflammatory Response Syndrome (SIRS)

At the 1991 consensus conference, the earlier Sepsis-1 definition was developed and SIRS criteria were established. Four SIRS criteria were defined, namely tachycardia (heart rate >90 beats/min), tachypnoea (respiratory rate >20 breaths/min), fever or hypothermia (temperature >38 or <36°C), and leukocytosis, leukopenia, or bandemia (white blood cells >1,200/mm3, <4,000/mm3 or bandemia ≥10%) (95).

This definition placed the systemic hyperinflammatory response at center stage. Patients meeting two or more of these criteria fulfil the definition of SIRS. Furthermore, Sepsis-1 was defined as infection or suspected infection leading to the onset of SIRS (96). The Sepsis-1 (95) and Sepsis-2 (5) guidelines established the definition of sepsis and related conditions that currently many clinicians use in everyday practice.

In the past 20 years, research has revealed that many patients develop acute organ dysfunction in response to infection, but without a measurable inflammatory excess (i.e. without the systemic inflammatory response syndrome [SIRS]).

SIRS in recent years has been criticized for its lack of specificity, prognostic value, and general utility (93,97). Due to these concerns, the recent Sepsis-3 guidelines encourage the use of the Quick Sepsis-related Organ Failure Assessment (qSOFA) when screening for sepsis (15).

Temperature	>38 or <36°C
White blood cell count	>12,000 or <4000/mm^3
Heart rate	>90 beats/min
Respiratory rate	>20 breaths/min or $PaCO_2$ mmHg

Figure 7. Systemic inflammatory response syndrome (SIRS) criteria
Two or more of the following criteria equates to a positive SIRS score.
[Retrieved from Bone *et al*. (95)]

1.1.7.3. Quick SOFA

The introduction of the quick sequential organ failure assessment or qSOFA score, attempted to improve the recognition of high-risk patients, as early as possible, by using basic clinical criteria at the bedside instead of complex biomarkers. It uses three criteria, assigning one point for low blood pressure (Systolic Blood Pressure ≤100 mmHg), high respiratory rate (≥22 breaths per min), or altered mentation (Glasgow coma scale<15). A score of at least two points is considered positive.

Several studies have revealed the correlation between a positive qSOFA and poor outcome in patients with sepsis (98). Recent publications have criticized the qSOFA score in terms of its diagnostic accuracy in comparison with early warning scores and other combinations of biomarkers and sepsis assessment criteria (93,94,99).

1.1.7.4. NEWS2

The National Early Warning Score 2(NEWS2) is an early warning system (EWS), that has become widely adopted in the UK's National Health Service in recent years, as a stratification tool to assess and monitor the clinical condition of in-hospital patients (92).

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Figure 8. The NEWS2 scoring system
[Retrieved from Royal College of Physicians (100)]

It is based on a simple aggregate scoring system, in which a score is allocated to physiological measurements. The data is readily accessible to clinicians as it already recorded in routine practice, when patients present to or are being monitored in hospital (94,101).

The NEWS measures six physiological parameters forming the foundation of the scoring system: respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness or new confusion and temperature. 0 to 3 points are allocated to each of seven clinical variables (six physiological, plus a weighting score for supplemental oxygen) (100).

The NEWS2 has demonstrated superior discrimination of acute deterioration compared to other early warning systems (EWS) (92).These tools are track and trigger systems of physiological parameters, which allow for the early detection of patient deterioration at many healthcare levels (pre-hospital, emergency department and wards) and enable triggering of an appropriate level of care (99).

The use of these scores has also led to sepsis alert systems, in which patients considered to be at high risk of critical illness are prioritized and treated according to sepsis bundles (94). It is the recommendation by the Royal College of Physicians that the NEWS2 be used as the primary tool of assessing illness severity and risk of deterioration in all patients, including those with suspected sepsis (100).

1.1.7.5. Comparison of criteria parameters

There is a certain degree of overlap in terms of parameters employed by all scores under assessment (NEWS2, SIRS and qSOFA) (Figure 9). There are three qSOFA parameters (respiration rate, systolic blood pressure and level of consciousness) that are measured by the updated NEWS2, which as of 2017 includes new confusion (100) (Figure 9). The NEWS2 supplements these three key parameters with the addition of measures of acute illness severity, i.e. oxygen saturation, pulse rate and temperature, as well as weighing the effects of oxygen therapy (94,97,100).

To compare overlapping parameters, measured qSOFA values in a particular patient revealing only mild tachypnea and moderate hypotension, could show a qSOFA of 2 and the NEWS2 score of only 4 and therefore be below the recommended critical trigger NEWS2 score threshold of 5 (Figure 9). This is most unlikely, as it assumes no additional abnormalities in oxygen saturation, pulse rate or temperature, any of which would increase the NEW score to 5 or more. In all other cases in which the qSOFA is 2, for instance a higher respiration rate or lower blood pressure, would bring the NEWS2 score to at least 5, as would any cases where

new confusion or any other acute alteration in mentation was apparent (94,100) (Figure 9). This conclusion is supported by a study undertaken at University College London Hospital that demonstrated that in every patient with a qSOFA score of 2 or more, there was a NEW score of 5 or more (100).

The additional parameters measured in the NEWS2 would be expected to augment the detecting abilities to identify patients at risk, compared with qSOFA. Various studies have demonstrated support for this hypothesis, finding that NEWS2 was superior to qSOFA in predicting adverse outcomes and that both stratification systems were superior to the SIRS criteria (92–94,100,101).

Parameters	qSOFA Cut-offs	NEWS2 Cut-offs	NEWS2	qSOFA
Respiration rate (RR)	≥22/min	22–24/min	2	1
(breaths/min)		≥25/min	3	1
Systolic Blood Pressure (SBP)	≤100 mmHg	91–100 mmHg	2	1
(mmHg)		≤90 mmHg	3	1
Altered mentation	GCS<15	New confusion plus delirium	3	1
(3-15)		Any reduction in GCS	3	1

Figure 9. The three overlapping qSOFA and NEWS2 parameters
[Adapted from Royal College of Physicians (100)]

Regarding prognostic value, it has been reported that even a single NEWS2 calculated from the first set of observations was predictive of adverse outcomes. In this analysis, Corfield *et al.* showed patients with a NEWS2 of 5 or 6 had twice the mortality rate of those with a NEWS2 of 0 to 4. Those with scores of 5 or more had nearly three times the combined adverse outcomes of ICU admission and/or mortality compared with those with a NEWS2 of 0 to 4 (102).

1.1.7.6.1. Determining the relevant thresholds for indicators of likely sepsis

The defined NEWS thresholds for the assessment of acute illness were derived from qSOFA development data. qSOFA scores, when measured in patients with infection, correlate very well with the agreed international consensus or 'gold standard' for scoring of illness severity in sepsis using the full SOFA criteria (3,15).

A qSOFA score of 2 is a critical threshold developed and outlined by the sepsis-3 taskforce. The three key qSOFA parameters defined were used in the development of the more comprehensive NEWS2 system. Taking this into consideration, a NEWS2 of 5 or more in patients with a known infection, signs or symptoms of infection, or at high risk of infection,

has been suggested by the Royal College of Physicians to most likely represent sepsis and therefore require a rapid escalation of clinical care, confirmatory investigations and urgent treatment (100).

Other studies have evaluated NEWS2 cut-offs of ≥4 and ≥8 for moderate and high-risk categories (93). Regardless, it must be emphasized that a raised NEWS2 (i.e. 5 or more) in a patient with signs and symptoms of infection, or clinical deterioration in a patient at high risk of infection, should always prompt the question 'Is this sepsis?'(100). In addition, if circumstantially, a NEWS2 of 5 or more is not specific for sepsis/septic shock, the heightened score warrants urgent escalation of care in all deteriorating patients regardless.

2. OBJECTIVES

2.1. Aim

The aim of this study was to test the sensitivity (true positive vs. false negatives) of various screening/diagnostic tools (SIRS, NEWS2 and qSOFA) and laboratory parameters (LAC, PCT, CRP) in detecting sepsis/septic shock (S/SS) at ICU admission. An additional goal was the assessment of prognostic value of detection tools in predicting overall mortality.

2.2. Hypothesis

1. NEWS2 will have higher sensitivity in detecting sepsis and/or septic shock in comparison to qSOFA and SIRS
2. NEWS2 will have a higher prognostic value in predicting overall mortality, compared to qSOFA and SIRS.

2.3. Primary Outcomes

The primary outcome was to test the sensitivity (true positives vs. false negatives) of detection tools (SIRS, NEWS2 and qSOFA) and laboratory parameters (LAC, PCT, CRP) in identification of sepsis/septic shock at ICU admission.

2.4. Secondary Outcomes

The secondary outcome was the prognostic value of stratification scores in predicting overall mortality at admission to the intensive care unit.

3. SUBJECTS AND METHODS

3.1. Study design

This retrospective study was conducted at the University of Split School of Medicine and Department of anesthesiology and intensive care at University Hospital of Split, Firule, over a period from January to July 2020. Study protocol was approved by the Ethics Committee of the University of Split School of Medicine and Ethics Committee of the University Hospital of Split.

3.2. Subjects

A total of 52 patients who met inclusion criteria were incorporated in the study. All patients were admitted to the ICU in 2018 and had a final diagnosis of sepsis or septic shock. Exclusion criteria were patients <18 years old, prisoners, pregnant women and epileptic seizure cases. Furthermore, 3 patients were excluded due to the missing of necessary data from the first 8 hours of admission.

3.3. Sample collection and laboratory analysis

The study material was collected at the Department of Anesthesiology, Reanimation and Intensive care at the University hospital of Split, KBC Firule. Materials gathered from computer databases and department archives, including discharge letters from previously discharged departments, ICU admission letters, inpatient files and ICU discharge letters. The data collected, displayed in Figure 10, was inserted and reviewed in Microsoft excel spread sheets. Vital signs were derived from ICU admission letters or in combination with previous departments (i.e. surgical, medical or emergency) discharge letters.

Laboratory parameters used were the first tests done upon admission to the ICU, all within the first 8 hours of admission. Blood samples for biomarkers (PCT, C-reactive protein [CRP] and lactate) were also taken within the first 8 h of ICU admission. The data of the patients, including demographic characteristics, vital signs, physiological parameters, cause of hospitalization, department pre-ICU admission, need for mechanical ventilation, mortality rates, and SOFA scores were recorded (Figure 10). Laboratory parameters, vital signs and scoring systems were based on first tests done upon admission to the ICU, all within the first 8 hours of admission.

Physical signs recorded:	Laboratory values recorded:
SpO2 (%), Air or O2	WBCs, Platelets
FiO2	Bilirubin
PaCO2(kPa), Pa02(kPa)	Creatinine
BP, Systolic BP, MABP	Procalcitonin
Pulse	CRP
Temperature	Lactate
Additional: use of Vasopressors was recorded	

Figure 10. Physiological and laboratory parameters measured
SpO2- Oxygen saturation percentage, FiO2-Fraction of inspired oxygen, Pa–Partial pressure, BP-blood pressure, MABP-mean arterial blood pressure, WBC-white blood cells, CRP-C-reactive protein

3.4. Sepsis scoring systems

Our target measure was to assess the sensitivity of scoring systems and markers to detect patients with sepsis/septic shock. Three scoring systems were selected for statistical comparison: SIRS (95) (Figure 7), qSOFA (3) and NEWS2 (Figure 8) (100). Previous studies have identified NEWS2 as high-performance, easily calculable and useful for both inpatients and patients in the emergency department (93). MedCalc online resource was employed for the calculation of sepsis stratification scores (SIRS, qSOFA and NEWS2). Increased respiratory rate was in the vast majority of cases not recorded numerically, rather as “tachypneic”, or “tachypnea”, this was according to general consensus noted as equivalent to a respiratory rate in excess of 20 breaths per minute. Pre-operative Glasgow coma scale (GCS) data was supplemented for GCS values for patients admitted intubated or sedated or both, especially in surgical patients. The AVPU (Alert, Voice, Pain, Unresponsive) scale is required for the calculation of NEWS2; however, our data only included GCS scores and thus AVPU equivalents were calculated using GCS data.

3.5. Statistical analysis

By using the medical history and discharge papers of the patients, the parameters needed were analyzed and shown in figures and tables. Microsoft Excel and Microsoft Word were used to make the tables and figures. Statistical software MedCalc (Ostend, Belgium; version 11.5.1.0) for Windows was used for statistical data analysis. Data were presented as means ± standard deviation for continuous variables and as whole numbers and percentage for categorical variables. T-tests were used for analysis used for comparison of categorical variables, while diagnostic test evaluations provided individual test sensitivities. The statistical significance was defined as $P<0.05$.

4. RESULTS

There were 52 septic patients admitted to the ICU Firule during the study period of which 32 (61.54%) patients had an end diagnosis of sepsis, while 20 (38.46%) had septic shock (Table 4 and Table 5). The mean age of patients was 65.46 (±15.41), while those with end point sepsis or septic shock had average ages of 63.91(±16.69) and 67.95 (±12.41), respectively (Table 4). There was a mortality rate of 43.3% overall, of which 45.5% of patients were diagnosed with sepsis, compared to 54.5% with septic shock (Table 5). The mortality rate in patients with sepsis was 31.25% and 60% amongst those with septic shock (Table 4).

The sensitivities for the detection of S/SS were SIRS=61.90% (95% CI 45.64 -76.43), NEWS2=82.35% (95% CI 69.13- 91.60) and qSOFA=36.00% (95% CI 23.62 – 51.04) (Table 1.). Pairwise comparisons were then conducted between SIRS, NEWS2 and qSOFA. For detecting S/SS (Table 1.), NEWS2 had a greater sensitivity than both SIRS (82.35% vs. 61.90, *P*=0.0206) and qSOFA (82.35% vs. 36%, *P*<0.0001). SIRS outperformed qSOFA by a large margin, with sensitivities of 61.90% vs. 36% (*P*=0.0086), respectively.

Table 1. Sensitivities of detection tools and comparative significance

	SIRS	***NEWS2***	***qSOFA***
Sensitivity*	61.90% (45.64 -76.43)	82.35% (69.13- 91.60)	36.00% (23.62 – 51.04)
***P* compared to SIRS †**	-	0.0206	0.0086
***P* compared to NEWS2 †**	0.0206	-	<0.0001
***P* compared to qSOFA †**	0.0086	<0.0001	-

* Diagnostic test evaluation
†Chi-squared for independent samples
95% CI within brackets
SIRS - Systemic Inflammatory Response Syndrome), NEWS2 - National Early Warning Score 2, qSOFA - Quick Sequential Organ Failure Assessment

In terms of biomarkers, CRP was the most sensitive (90.38%, 95%CI 78.97-96.80) in identifying sepsis/septic shock, outperforming PCT (71.43%, 95% CI 53.7-85.36) and lactate (44.9%, 95% CI 30.67-69.77) (Table 2.). In comparison, CRP (90.38% vs. 44.9%, *P*<0.0001) and PCT (71.43% vs. 44.9%, *P*=0.0164) demonstrated markedly more sensitive recognition of S/SS than lactate. CRP outperformed PCT, with sensitivities of 90.38% vs. 71.43% (*P*=0.0225), respectively (Table 2.).

Table 2. Sensitivities of biomarkers and comparative significances

	LAC N=49	CRP N=52	PCT N=35
Sensitivity*	44.9% (30.67-59.77)	90.38% (78.97-96.8)	71.43% (53.7-85.36)
***P* compared to LAC †**	-	<0.0001	0.0164
***P* compared to CRP †**	<0.0001	-	0.0225
***P* compared to PCT †**	0.0164	0.0225	-

*Diagnostic test evaluation
†Chi-squared test for independent samples
95% CI within brackets.
LAC – Lactate, CRP - C-reactive protein, PCT - Procalcitonin

There were no statistically significant differences in predicting S/SS mortality found amongst stratification scores. Scores of ≥2 for qSOFA, SIRS and ≥5 for NEWS2, predicted overall mortality rates of 42.11% (20.25-66.5), 41.67% (25.51-59.24) and 40.91% (26.34-56.75), respectively (Table 3).

Table 3. Mortality prediction of stratification scores

	SIRS	NEWS2	qSOFA
Mortality*	41.67% (25.51-59.24)	40.91% (26.34-56.75)	42.11% (20.25-66.5)
***P* compared to SIRS†**	-	0.946	0.975
***P* compared to NEWS2†**	0.946	-	0.930
***P* compared to qSOFA†**	0.975	0.930	-

*Diagnostic test evaluation
†Chi-squared test for independent samples
95% CI within brackets
SIRS - Systemic Inflammatory Response Syndrome), NEWS2 - National Early Warning Score 2, qSOFA - Quick Sequential Organ Failure Assessment

Comparisons between patients with sepsis (N=32) and those with septic shock (N=20) were conducted. Mortality in septic patients was notably lower than those with septic shock, 31.25% vs. 60% (*P*=0.043), respectively (Table 4.1.). Age, gender, requirement for mechanical ventilation, along with measured physiological parameters did not show any significant differences (Table 4.). This was also evident for laboratory parameters measured between groups. Patients in septic shock had a greater requirement for vasopressors, which was expected, 70% vs. 25% (*P*=0.001), respectively (Table 4.1.).

Regarding mean biomarker concentrations, septic shock patients had significantly higher concentrations of lactate (3.39 ±1.67 vs. 1.97±1.19, *P*=0.0008) and PCT (36.38±38.69 vs.14.35±29.78, *P*=0.025) (Table 4.2.). No significant differences in CRP were found between septic and septic shock patients, although interestingly mean CRP concentration was greater in those with an end diagnosis of sepsis (Table 4.2.). Furthermore, measured detection scores SIRS (1.84 ±0.77 vs. 2.2 ±1.2, *P*=0.192), NEWS2 (7.81±3.19 vs. 8.4±3.69, *P*=0.544) and qSOFA (1.16±0.88 vs. 1.25±0.85, *P*=0.717) also showed no significant differentiation between sepsis and septic shock (Table 4.2.).

Parameters between survivors and non-survivors were compared. In terms of baselines characteristics, non-survivors were predominantly older (71.32 ±10.37 vs. 61.79 ±17.01, *P*=0.020) and had a proportionally greater requirement for mechanical ventilation (86.4% vs. 56.7%, *P*=0.023) (Table 5.1.). 73.3% (N=22) of survivors (N=30) had an end point diagnosis of sepsis, compared to 45.5% (N=10) of non-survivors (*P*=0.018) (Table 5.1.). Of non-survivors, 54.5% (N=12) had septic shock in comparison to 26.7% (N=8) of the surviving patients (*P*=0.043)

No significant differences were found regarding the physiological parameters measured, except for survivors who demonstrated higher oxygen partial pressures (PaO2), (17.39 ±6.72 vs. 11.11 ±3.09, *P*=0.002) (Table 5.2.). Similarly, laboratory parameters showed only a significant difference in serum creatinine between the two groups (114.33 ±86.42 vs. 195.73 ±166.37, *P*=0.025), survivors and non-survivors, respectively.

Lastly, mean biomarker concentrations PCT (*P*=0.859), Lactate (*P*=0.432), CRP (*P*=0.475) and sepsis detection scores SIRS (*P*=0.661), NEWS2 (*P*=0.731) and qSOFA (*P*=0.936) failed to show any significant statistical differentiation between survivors and non-survivors (Table 5.2.).

Table 4.1. Demographics, physiological and laboratory parameters of patients with sepsis vs. septic shock.

	All Patients (N=52)	Sepsis (N=32)	Septic Shock (N=20)	*P* *
Age	65.46 (±15.41)	63.91 (±16.69)	67.95 (±12.41)	0.355
Male	35 (67.31)	24 (75.00)	11 (55.00)	0.138
rMV	36 (69.2%)	24 (75.00)	12 (60.00)	0.258
Mortality	22 (43.31)	10 (31.25)	12 (60)	**0.043**
Physiological Parameters				
SpO2 (%)	93.73 (±6.65)	93.41 (±7.91)	94.25 (±4.31)	0.665
rO2	45 (88.24)	28 (87.50)	17 (85.00)	0.799
PO2 (kPa)	14.73 (±6.22)	15.33 (±5.87)	13.78 (±6.93)	0.348
PCO2 (kPa)	5.16 (±1.13)	4.93 (±1.13)	5.53 (±1.07)	0.063
Temp (°C)	36.42 (±0.90)	36.56 (±0.96)	36.21 (±0.79)	0.178
Heart rate (/min)	102.60 (±27.70)	102.41 (±31.40)	102.9 (± 22.18)	0.951
SBP (mm/Hg)	113.44 (±29.47)	115.28 (±27.83)	110.5 (± 33.13)	0.578
MAP (mm/Hg)	82.68 (±19.56)	84.05 (±17.55)	80.5 (±23.17)	0.533
GCS	11.10 (±4.43)	10.53 (±4.79)	12 (±3.84)	0.252
Laboratory Parameters				
Creatinine	148.77 (±130.23)	132.63 (±126.77)	174.6 (±138.04)	0.267
Bilirubin (umol/L)	24.25 (±33.96) N=48	19.9 (±15.11) N=29	30.89 (±51.40) N=19	0.26
WBCs (x109/L)	15.44 (±10.86)	14.58 (±9.76)	16.81 (±12.81)	0.481
Platelets (x109/L)	246.65 (±151.31)	249.06 (±128.75)	242.8 (±188.65)	0.887
rVSP	22 (42.31)	8 (25)	14 (70)	**0.0016**

Data is presented as mean±standard deviation or number and percentages
*t-test for independent samples
rMV - Required Mechanical ventilation, SpO2 – Saturation percentage of oxygen, rO2 – Required supplemental oxygen, PO2 – partial pressure of oxygen, PCO2 – partial pressure of carbon dioxide, Temp – Temperature, SBP - Systolic blood pressure, MAP – Mean arterial pressure, GCS – Glasgow coma scale, WBCs – White blood cells, rVSP - required vasopressor

Table 4.2. Biomarkers and detection tools in patients with sepsis vs. septic shock.

	All Patients (N=52)	Sepsis (N=32)	Septic Shock (N=20)	*P* *
Biomarkers				
PCT (ng/mL)	23.80 (±34.63) N=35	14.35 (±29.78) N=20	36.38 (±38.69) N=15	**0.025**
LAC (mmol/L)	2.50 (±1.54) N=49	1.97 (±1.19) N=30	3.39 (±1.67) N=19	**0.0008**
CRP (mg/L)	193.56 (±117.45)	205.31 (±120.11)	174.76 (±116.67)	0.371
Detection Tools	(N=52)	(N=32)	(N=20)	
NEWS2	8.04 (±3.37)	7.81 (±3.19)	8.4 (±3.69)	0.544
SIRS	1.98 (±0.96)	1.84 (±0.77)	2.2 (±1.2)	0.192
qSOFA	1.19 (±0.86)	1.16 (±0.88)	1.25 (±0.85)	0.717

Data is presented as mean±standard deviation or number and percentages
*t-test for independent samples
PCT – Procalcitonin, CRP – C-reactive protein, LAC – Lactate, NEWS2 – National early warning score 2, SIRS – Systemic inflammatory response syndrome, qSOFA – Quick sequential organ failure assessment

Table 5.1. Demographics, physiological and laboratory parameters in patients with S/SS, survivor's vs. non-survivors

	All Patients (N=52)	Survivors (N=30)	Non-survivors (N=22)	*P* *
Age	65.46 (±15.41)	61.79 (±17.01)	71.32 (±10.37)	**0.020**
Male	35 (67.31)	21 (70)	14 (63.64)	0.632
rMV	36 (69.2%)	17 (56.67)	19 (86.36)	**0.023**
Sepsis	32 (61.54)	22 (73.33)	10 (45.45)	**0.018**
Septic Shock	20 (38.46)	8 (26.66)	12 (54.54)	**0.043**
Mortality	22 (43.31)	0	22 (43.31)	
Physiological Parameters (units, SD)				
SpO2 (%)	93.73 (±6.65)	94.74 (±6.70)	92.36 (±6.64)	0.209
rO2	45 (88.24)	24 (80.00)	21 (95.45)	0.123
PaO2 (kPa)	14.73 (±6.22)	17.39 (±6.72)	11.11 (±3.09)	**0.002**
PaCO2 (kPa)	5.16 (±1.13)	5.03 (±1.15)	5.35 (±1.12)	0.321
Temp. (°C)	36.42 (±0.90)	36.48 (±0.86)	36.34 (±0.97)	0.585
Heart rate (/min)	102.60 (±27.70)	104.93 (±30.90)	99.41 (±23.74)	0.487
SBP (mm/Hg)	113.44 (±29.47)	111..97 (±28.34)	115.45 (±32.74)	0.683
MAP (mm/Hg)	82.68 (±19.56)	82.75 (±18.98)	82.59 (±21.23)	0.977
GCS	11.10 (±4.43)	11.23 (±4.61)	10.91 (±4.37)	0.801
Laboratory Parameters				
Creatinine (umol/L)	148.77 (±130.23)	114.33 (±86.42)	195.73 (±166.37)	**0.025**
Bilirubin (umol/L)	24.25 (±33.96) N=49	17.90 (±13.39) N=29	33.95 (±51.30) N=19	0.106
WBCs (x109/L)	15.44 (±10.86)	17.71 (±12.75)	12.35 (±7.07)	0.081
Platelets (x109/L)	246.65 (±151.31)	244.5 (±123.41)	249.59 (±188.80)	0.906
rVSP	22 (42.31)	12 (40)	10 (45.45)	0.6971

Data is presented as mean±standard deviation or number and percentages
*t-test for independent samples
rMV - Required Mechanical ventilation, SpO2 – Saturation percentage of oxygen, rO2 – Required supplemental oxygen, PO2 – partial pressure of oxygen, PCO2 – partial pressure of carbon dioxide, Temp – Temperature, SBP - Systolic blood pressure, MAP – Mean arterial pressure, GCS – Glasgow coma scale, WBCs – White blood cells, rVSP - required vasopressor

Table 5.2. Biomarkers and detection tools in patients with S/SS, survivor's vs. non-survivors

	All Patients (N=52)	Survivors (N=30)	Non-survivors (N=22)	*P* *
Biomarkers				
PCT (ng/mL)	23.80 (±34.63) N=35	22.75 (±37.11) N=18	24.90 (±34.02) N=17	0.859
LAC (mmol/L)	2.50 (±1.54) N=49	2.35 (±1.40) N=28	2.70 (±1.76) N=21	0.442
CRP	193.56 (±117.45)	183.38 (±118.93)	207.44 (±119.48)	0.475
Detection Tools	(N=52)	(N=30)	(N=22)	
NEWS2	8.04 (±3.37)	7.90 (±3.1)	8.23 (±3.77)	0.731
SIRS	1.98 (±0.96)	1.93 (±0.83)	2.05 (±1.13)	0.661
qSOFA	1.19 (±0.86)	1.20 (±0.81)	1.18 (±0.96)	0.936

Data is presented as mean±standard deviation or number and percentages
*t-test for independent samples
PCT – Procalcitonin, CRP – C-reactive protein, LAC – Lactate, NEWS2 – National early warning score 2, SIRS – Systemic inflammatory response syndrome, qSOFA – Quick sequential organ failure assessment

5. DISCUSSION

In this retrospective study we found that NEWS2 is significantly more sensitive than both SIRS and qSOFA in detecting sepsis and septic shock at ICU admission. Significant statistical diffreences were not demonstrated between scoring systems for prediction of overall mortality. The assessment of biomarkers revealed that CRP has a greater sensitivity in identifying S/SS, in comparison to PCT and LAC. The combination of effective and accurate scoring systems is essential to aid in the diagnosis of S/SS to improve patient outcomes and mortality, as early identification leads to timely intervention.

Sepsis and septic shock have high mortality rates, that require increasingly effective prevention strategies to accompany the newly envisioned paradigms. Early recognition leading to the administration of antibiotics provides the best outcomes, as for each elapsed hour between presentation and antibiotic administration, is associated with a 9% increase in the odds of mortality in patients with sepsis (103). As the clinical picture for sepsis can vary at all points across the vast spectrum of disease severity, tools (scoring systems and biomarkers) to aid in the accurate identification of S/SS are crucial to the diagnostic process. Other studies have assessed various combinations of inclusively and/or exclusively biomarkers and stratification systems.

Our study, as far as we know, is the first in which the NEWS2 score has been implemented for diagnostic purposes at ICU admission. The findings that NEWS is more sensitive, than both SIRS and qSOFA (82.35% vs. 61.9%, P=0.0206 and 82.35% vs. 36%, P<0.0001), have been shown in numerous studies (93,94,101). A study undertaken by Usman *et al.* in an emergency department triage environment found NEWS2 to be more accurate, when compared with both SIRS and qSOFA, for the early detection of S/SS and sepsis-related mortality. Moreover, the authors found SIRS to be superior to qSOFA for the prediction of S/SS (93). NEWS2 and SIRS provide better sensitivity for the detection of S/SS at ICU admission compared with qSOFA. Although our study did not encompass assessments of specificity, other studies have found that NEWS2 provides superior specificity over SIRS without any significant difference in sensitivity. Furthermore, it has been consistently shown in various studies qSOFA favors specificity over sensitivity (18,93,97,99,104,105).

Possible reasons, as to why qSOFA fails to achieve high sensitivity, is due to the omission of important variables (i.e. heart rate and temperature), informative physiological response signals, that often precede and are correlated with clinical deterioration (102). Treatment may be delayed while waiting for organ dysfunction to develop, leading to poorer outcomes, lengthened ICU stay and overall higher mortality (93).

It is evident from various publications, that NEWS2 outperforms SIRS. Authors have reasoned this to be likely due to the inclusion of altered mental status, blood pressure, and oxygenation, which are readily available indicators of end- organ dysfunction. This aspect of availability of the NEWS2 is critical in terms of effective and time efficient diagnosis, as early administration of antibiotics is the most important influencer of outcomes in S/SS. The NEWS2 has no reliance on laboratory values and is fully calculable at the beside in settings of emergency triage, admission to general wards and the intensive care unit admission. In contrast, SIRS relies on laboratory values and therefore leads to an inevitable delay in score formulation, thereby prolonging the recognition and eventual treatment of S/SS (93).

Different cut-off sensitivities for NEWS2 were assessed, as previous studies found NEWS2 may offer scoring flexibility relative to SIRS and qSOFA, by allowing for the creation of multiple severity categories (97,100,102). It was reported that stratification of risk categories could improve accuracy and to separate patients according to specific treatment pathways. For example, the positive predictive value for so called "low risk" patients (NEWS2 ≤3) was <3.3%, "moderate risk" patients (NEWS2 between 4 and 8) was 5.1 to14.7% and "high risk" patients (NEWS2 ≥9) was 17.8% to 50%. Patients flagged as "moderate risk" may indicate the need for obtaining a lactic acid level, whereas patients flagged as "high risk" may benefit from the rapid mobilization of bundled resources and early ICU consultation (7,93,100). Usman *et al*. went further, showing that NEWS2 ≥4 is more specific and the sensitivity is non-inferior, compared with SIRS ≥2 for detection of S/SS and sepsis-related mortality (93). Our study demonstrated a higher degree of sensitivity for a NEWS2 cut-off of ≥4, in comparison to SIRS≥2 and qSOFA ≥2 for the detection of S/SS (Refer to Table 1, Table 2 and Table 3) in the Supplement).

In a study conducted by Churpek *et al*., it was found that early warning scores are more accurate and provide an earlier response than qSOFA and SIRS, for predicting mortality and ICU transfer for patients outside of the ICU with suspected infection (106). In our study, no statistical significance was observed regarding sepsis-related mortality prediction, although other publications have found that in general, table-based aggregate weighted systems, such as NEWS2, were more predictive and robust compared with tally-based single parameter scores, such as qSOFA and SIRS. This is suggested to be due to more cut-off points, bi-directional scoring (e.g. points for both hypothermia and fever) and the ability of EWS to capture non-linear relationships (93).

NEWS2 was developed for the detection of clinical deterioration in inpatients and not for the detection of sepsis. However, SIRS and qSOFA were created as simple bedside screening tools and are easier to calculate than NEWS2 and therefore, not fully suited for the role to which it has been appropriated. This is reflected in some of the NEWS2 components that may be inappropriate in the context of sepsis. Furthermore, NEWS2 maybe best implemented using automated emergency medical response (EMR)-based clinical tool calculators, which has been the norm in the majority of UK hospitals (93,100).

We hypothesize, that adjusting some of these variables or deriving a de novo sepsis scoring system may lead to improvements, utilizing the superior diagnostic accuracy of the NEWS2, while maintaining the relative simplicity of scores, such as qSOFA for the specific detection on patients with S/SS.

CRP and PCT are by far the most widely used and studied biomarkers, whose transient elevations during sepsis are reflective of a real-time host response (70). PCT is considered superior to CRP in numerous studies, although being more specific than CRP, it is not a definitive test for diagnosing sepsis, as levels can also be increased in a range of other conditions (68,69). Contrarily, in our study CRP outperformed PCT, with a higher sensitivity in detecting S/SS. This could be due to the fact, that 17 patients were missing PCT concentrations, as they were not available within the 8h period of the studies data collection cut-off. This may be further reasoned as studies have shown that among patients admitted for suspected sepsis, procalcitonin (PCT) best predicts septicemia, but CRP preforms better in identifying those with clinical infection (71). As our study identified patients with an end diagnosis of sepsis, those admitted had not necessarily had disease progression to sepsis, but rather an underlying clinical infection, while some may have developed the infection and transitioned to S/SS during their stay in the ICU.

CRP has been found to perform relatively inaccurately in diagnostic tasks detecting sepsis compared with PCT. Numerous reviews indicate that the sensitivity and specificity of both CRP (ranging from 35 to 100% and from 18 to 84%, respectively) and PCT vary significantly(ranging from 42 to 100% and from 48 to 100%, respectively) (69,77,78,80,83). In addition, some studies suggest that CRP levels increase in 4 to 6 h and reach peaks in 48 to72 h after the inflammatory onset, while PCT levels increase in 8 to 24 h and peak later than 24 h. Therefore, both PCT and CRP might still not be reliable enough as early indicators for sepsis to be used in this specific clinical context or as single parameters at admission (69).

A meta-analysis reported superior diagnostic performance of PCT over CRP in surgical and trauma patients with sepsis versus no sepsis, while further studies demonstrated its better correlation with the severity of illness in patients with sepsis (32). Overall, PCT, similar to CRP, may be more useful to rule out sepsis than to diagnose it and the combination of these two readily available biomarkers may improve their ability to exclude sepsis (70).

Regarding lactate, it was clear prior to study commencement that its specificity for S/SS is not adequate for the use of detection, it was used in our study as a baseline marker for comparison. Lactate levels, particularly associated with poor clearance, have been shown to be a predictor of mortality and are associated with mortality irrespective of the presence or absence of infection (18). In the presence of sepsis, where infection has not yet been confirmed, an immediate CRP, combined with PCT and NEWS2 may lead to a more accurate diagnosis and thus a more appropriate and individualized care of critically ill septic patients.

A recent study by Usman *et al.* supports the external validity of our results, since they had similar endpoint selection methods and showed comparable sensitivities of 91.3% versus 92.31% in our study for NEWS ≥3 and 84.5% versus 84.62% in our study for NEWS ≥5 (93). Our reported mortality rate for sepsis of 31.3% was just above the proportions reported by other studies of between 12% and 30%. In terms of septic shock, the mortality was much higher in our study (60%) compared to other much larger studies reporting morality rates between 18% and 46% (19,92–94,98,107).

The diagnosis of S/SS was chosen as the primary endpoint, rather than mortality, as previous researchers have encouraged the validation of qSOFA and NEWS for outcomes other than mortality (3,93,100). Many mortality-based scoring systems were created for risk stratification of inpatients and not for clinical decision-making, however, with the recent paradigm shift in how we think about sepsis, more emphasis is now placed on the timely decision to treat sepsis (1,18,74). Once this decision has been made, prognostication may not significantly affect the mainstays of sepsis treatment: early antibiotics, source control and cardiopulmonary optimization (93,103).

This was a small (n=52) retrospective single-center study with a predominately Caucasian population. Moreover, the retrospective study design may increase risk for misclassification biases and confounding. By calculating scores at admission, we diminished the effect of confounding actions by clinicians. However, endpoint determination is still subject to reviewer bias as it was established retrospectively and unblinded.

Unlike other similar studies, we did not define a patient group for those with 'suspected infection' and therefore could not obtain a complete picture of diagnostic accuracy. The assessment of specificity was beyond the scope of the study design. As far as we know, there is no concordance amongst authors on the definition of 'suspected infection', varying from one of systemic inflammatory response syndrome (SIRS) criteria to self-reported fever or chills (94). Patients were not excluded if admission was due to trauma. Exclusion of this population would have enabled narrowing of selection criteria, by omitting those with obvious traumatic causes of potential stratification score or biomarker elevation.

In summary, our study had limitations as sensitivities were measured by parameters obtained at admission, in a population of patients with end point diagnoses of sepsis or septic shock. Accordingly, direct correlation cannot be accurately obtained as patients may have developed sepsis or become inoculated by respective causative pathogens during ICU stay, as is often the case. 2% of all hospitalized patients develop sepsis during their stay, in comparison to ICU patients where numbers range anywhere from 6 to 30%, globally (14). Given that most departments routinely gather the inputs necessary for this analysis, our study should be easily reproducible at other institutions and various settings even outside the ICU.

6. CONCLUSION

Our retrospective analysis found that NEWS2 is a more sensitive scoring system than both SIRS and qSOFA for the early detection of S/SS. Regarding prognostic value of stratification scores measured, we did not find any statistical significance for the prediction of overall mortality. In terms of biomarkers, CRP was found to be the most sensitive marker for the detection of S/SS, while both CRP and PCT were found to be superior than lactate.

7. REFERENCES

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8. SUMMARY

Objectives: This study aimed to test the sensitivity (true positive vs false negatives) of various diagnostic tools (SIRS, NEWS2 and qSOFA) and laboratory parameters, lactate (LAC), procalcitonin (PCT) and C-reactive protein CRP) in detecting sepsis/septic shock (S/SS) at ICU admission. An additional goal was to assess prognostic value of detection tools in predicting overall mortality.

Subjects and methods: A total of 52 patients with S/SS were enrolled into this retrospectively conducted study, 32 (61.54%) had an end point diagnosis of sepsis, while 20 (38.46%) had septic shock. Overall, there was a mortality rate of 43.3%. Stratification scores were determined and further analyzed using MedCalc online resources and MedCalc for Windows, respectively. Biomarkers (CRP, PCT and LAC) and other biochemical parameters were determined by standard laboratory procedures.

Results: The sensitivities for the detection of S/SS were SIRS=61.90% (95% CI 45.64 -76.43), NEWS2=82.35% (95% CI 69.13- 91.60) and qSOFA=36.00% (95% CI 23.62 – 51.04). NEWS2 had a greater sensitivity than both SIRS (82.35% vs. 61.90, P=0.0206) and qSOFA (82.35% vs. 36%, P<0.0001). There were no statistically significant differences in predicting S/SS mortality found amongst stratification scores. In terms of biomarkers, CRP was the most sensitive (90.38%, 95%CI 78.97-96.80) in identifying sepsis/septic shock, outperforming PCT (71.43%, 95% CI 53.7-85.36) and lactate (44.9%, 95% CI 30.67-69.77)

Conclusion: This study confirmed that the NEWS2 is significantly more sensitive than SIRS and qSOFA in detecting sepsis and septic shock at ICU admission. No statistical significance was found for the prediction of mortality. Furthermore, regarding sepsis biomarkers, CRP demonstrated greater sensitivity in identifying S/SS, than PCT and LAC. Further studies are needed to clarify the combined roles of detection tools and biomarkers for the early identification of S/SS.

9. CROATIAN SUMMARY

Naslov: Procjena dijagnostičke osjetljivosti različitih sustava stratifikacije i biomarkera za identifikaciju sepse / septičkog šoka, prilikom prijema u JIL

Cilj: utvrđivanja osjetljivosti (tj. vjerojatnosti pozitivnog nalaza u bolesnih) različitih dijagnostičkih testova u bolesnika sa sepsom/septičkim šokom. Testirani su testovi probira (SIRS, NEWS 2 i qSOFA), kao i određeni laboratorijski parametri (laktati, prokalcitonin I C-reaktivni protein) kod prijama u jedinicu intenzivnog liječenja. Dodatni cilj je bio procjena prognostičke vrijednosti testova probira u predviđanju ukupne smrtnosti.

Bolesnici i metode: U ovo retrospektivno istrazivanje uklucena su ukupno 52 bolesnika sa S / SS uključena su u ovo retrospektivno provedeno istraživanje, njih 32 (61,54%) je imalo zavrsnu dijagnozu sepse, dok je njih 20 (38,46%) imalo dijagnozu septički šok. Sveukupno, stopa smrtnosti za sve bolesnike iznosila je 43,3%. Rezultati testova probira su analizirani pomoću mrežnih resursa MedCalc i MedCalc za Windows. Biomarkeri (CRP, PCT i LAC) i drugi biokemijski parametri određivani su standardnim laboratorijskim postupcima.

Rezultati: Osjetljivost na otkrivanje S / SS bila je SIRS = 61,90% (95% CI 45,64 -76,43), NEWS2 = 82,35% (95% CI 69,13 - 91,60) i qSOFA = 36,00% (95% CI 23,62 - 51,04), NEWS2 imao je veću osjetljivost od SIRS-a (82,35% nasuprot 61,90, P = 0,0206) i qSOFA (82,35% nasuprot 36%, P <0,0001). Nije bilo statistički značajnih razlika u predviđanju S / SS smrtnosti pronađenih među tri testa probira. U pogledu biomarkera, CRP je bio najosjetljiviji (90,38%, 95% CI 78,97-96,80) u identificiranju sepse / septičkog šoka, a potom slijede PCT (71,43%, 95% CI 53,7-85,36) i laktati (44,9%, 95% CI 30,67 - 69,77)

Zaključak: Ova studija potvrdila je da je NEWS2 značajno osjetljiviji test probira od SIRS-a i qSOFA u svrhu otkrivanja sepse i septičkog šoka prilikom prijema u JIL. Nije pronađena statistički značajna razlika među testovima glede predviđanja smrtnosti. Nadalje, što se tiče biomarkera za sepsu, CRP je u ovoj studiji pokazao veću osjetljivost u identificiranju S / SS, nego PCT i LAC. Potrebne su daljnje studije kako bi se razjasnila kombinirana uloga raznih "screening" testova i biomarkera za ranu identifikaciju S / SS.

10. CURRICULUM VITAE

Personal information

Name: Duje Bjelić

Date and place of birth: November 2nd, 1990, Rijeka, Croatia.

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Education:

2014-2020 Doctor of Medicine
University of Split School of medicine, Split, Croatia.

2009-2012 Bachelor of Health sciences: Majors - Neuroscience, Physiology and Pathology
University of Adelaide, School of Health Sciences, Adelaide, Australia.

2006-2008 Norwood Morialta High School, Adelaide, Australia

2004- 2006 Prva Sušačka Hrvatska Gimnazija, Rijeka, Croatia

Employment History:

2012-2014 Laboratory assistant, Clinpath Laboratories, Adelaide, Australia
2009-2013 Locum Physician assistant, GP Solutions, Adelaide, Australia

Clinical experience:

2020 Medical volunteer, Medical Volunteers International (MVI), Athens, Greece

Languages:

Croatian (mother tongue)
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11. SUPPLEMENT

Table 1. Comparison of cut-off sensitivities for NEWS2

Cut-offs	All Patients n=52	Sepsis n=32	Septic shock n=20
	Sensitivity*	Sensitivity*	Sensitivity*
1	-	-	-
2	98.08% (89.74-99.95)	100% (89.11-100)	95% (75.13-99.87)
3	94.23% (84.05-98.79)	96.88% (83.78-99.92)	-
4	92.31% (81.46-97.86)	93.75% (79.19-99.23)	90% (68.3-98.77)
5	84.62% (71.92-93.12)	84.38% (67.21-94.72)	-
6	73.08% (58.98-84.43)	65.62% (46.81-81.43)	85% (62.11-96.79)
7	65.38% (50.91-78.03)	59.38% (40.64-76.3)	75% (50.9-91.34)
8	57.69% (43.20-71.27)	50% (31.89-68.11)	70% (45.72-88.11)
9	48.08% (34.01-62.37)	46.88% (29.09-65.26)	50% (27.2-72.8)
10	36.54% (23.62-51.04)	34.38% (18.57-53.19)	40% (19.12-65.95)
11	28.85% (17.13-43.08)	31.25% (16.12-50.01)	25% (8.66-49.1)
12	15.38% (6.88-28.08)	15.62% (5.28-32.79)	15% (3.21-37.89)
13	5.77% (1.21-15.95)	3.12% (0.08-16.22)	10% (1.23-31.7)
14	-	-	-
15	-	-	-
16	1.92% (0.05-10.26)	-	5% (0.13-24.87)

*Diagnostic test evaluation
CI 95% in brackets

Table 2. Comparison of cut-off sensitivities for qSOFA. 95% CI in brackets

Cut-offs	All Patients n=52	Sepsis n=32	Septic shock n=20
	Sensitivity*	**Sensitivity***	**Sensitivity***
1	76.47% (62.51-87.21)	75% (56.6-88.54)	80% (56.34-94.27)
2	35.29% (22.43-49.93)	34.38% (18.57-53.19)	40% (19.12-63.95)
3	5.77% (1.21-15.95)	6.25% (0.77-20.81)	5% (0.13-24.87)

*Diagnostic test evaluation
CI 95% in brackets

Table 3. Comparison of cut-off sensitivities for SIRS

Cut-offs	All Patients n=52	Sepsis n=32	Septic shock n=20
	Sensitivity*	**Sensitivity***	**Sensitivity***
1	94.23% (84.05-98.79)	96.88% (83.78-99.92)	90.00% (68.3-98.77)
2	69.23% (54.90-81.28)	68.75% (49.99-83.88)	70.00% (45.72-88.11
3	30.77% (18.72-45.10)	18.75% (7.21-36.44)	50.00% (27.2-72.80)
4	3.85% (0.47-13.41)	-	10.00% (1.23-31.7)

*Diagnostic test evaluation
CI 95% in brackets