COMBINED USE OF QSOFA SCORE, LACTATE AND NLR AS AN EARLY PREDICTIRE OF SPESIS IN PAINENTS PRESENTING TO EMERGENCY DEPARTMENT

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ABBREVIATIONS

ED	Emergency Department
SS	Severe sepsis
SIRS	Systemic inflammatory response syndrome
qSOFA	Quick Sequential Organ function assessment
GCS	Glasgow Coma Scale
SBP	Systolic Blood Pressure
MAP	Mean arterial pressure
RR	Respiratory Rate
TLC	Total leucocyte count
DLC	Differential leucocyte count
NLR	Neutrophil: Lymphocyte ratio
ANC	Absolute Neutrophil Count
ALC	Absolute Lymphocyte Count
SD	Standard deviation
CI	Confidence interval
S	Survivor group
NS	Non survivor group
Sn	Sensitivity
Sp	Specificity
ROC	Receiver Operator Characteristic
PDH	Pyruvate Dehydrogenase

INTRODUCTION

Sepsis is the presence of life-threatening organ dysfunction caused by a dysregulated response of body to infection. Sepsis -3 is the new term adapted in 2016 task force convened by National societies including the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) to replace severe sepsis and septic shock. [Singer M 2016] Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of > 65mmHg and serum lactate level > 2 mmol/L (>18mg/dL) in absence of hypovolemia. The criteria to identify poor prognosis in sepsis is defined as presence of at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quick SOFA (qSOFA): respiratory rate (RR) of > 22/min, altered sensorium (GCS < 15) or systolic blood pressure (SBP) of < 90 mmHg. This is a rapid unaided, noninvasive, easy to perform assessment which can be performed anywhere within hospital like in emergency department, ICU and general hospital ward settings. Sepsis -3 is a sever disease with global burden of 48.9 million cases and 11 million sepsis-related mortality. Annual incidence of sepsis is approximately 19.4 million cases per year out of which 14.1 million require hospitalization. Mortality rate from sepsis ranges between 25% and 30% for severe sepsis and 40% and 70% for septic shock. [Lever A 2007] It has been reported to be the second leading cause of death in non-coronary intensive care units, and overall, it is the tenth leading cause of death. Sepsis is classifying into two phases on the basis of duration - Early phase and late phase. Early phase is initial 5 days of illness followed by the late phase. [Rich'e F 2015] Singer et al stated that early recognition of sepsis is essential for reducing the

high mortality and morbidity rate in patients with suspected infection presented to ED. [Singer et al 2015]

Researchers are always in search of definite clinical and laboratory parameters to consider them as biomarkers that could be accurate and reproducible and should be used as a diagnostic tool for disease identification or abnormal conditions associated with disease as well as for staging disease, its prognosis and response to intervention. There are numerous cellular processes involved in sepsis hence finding a reliable and specific diagnostic biomarker is a challenging task for scientists till date. More than 1000 different molecules have been identified and suggested to be used as useful biomarkers of sepsis in past decade. The hematological parameters supposed to be used as biomarkers are under study like TLC, ANC, ALC, NLR, Platelet count (PLC), Platelet: Lymphocyte ratio (PLR), Erythrocyte Sedimentation Rate (ESR) and Peripheral blood smear examination for toxic granules and vacuoles. Biochemical markers studied for sepsis and sepsis related complications include ABG, lactate, interleukins, cytokines, Procalcitonin, C-reactive protein, Angiopoietins, Endocans, leukocyte surface antigen CD64, triggering receptor expressed on myeloid cells 1(TREM-1), Circulating cell – free DNA (cf-DNA), Programmed cell death receptor -1 (PD-1), B and T-lymphocyte attenuator (BTLA), Cytotoxic T-lymphocyte antigen -4 (CTLA-4) etc. The individual role of these molecules in relation to sepsis is well explained in several studies but no one had proven effectively as diagnostic or prognostic tool. [Faix JD 2013]

Blood culture is the gold standard microbiological investigation used for diagnostic conformation since long ago but the major drawback is its time consumption (3-5days)

and false negative result when patient has previously received antibiotics. This is a major concern for clinicians while handling a case with suspected infection in ED during which patients' morbidity and mortality progresses rapidly.

As per the sepsis 3 guideline, quick sequential organ failure assessment (qSOFA) score has become an important clinical tool that can be utilized at bedside for identification of sepsis and predict mortality. It gives an alarm meant by **"do not loose time".**

The qSOFA score consists of three clinical elements: hypotension (SBP < 90 mmHg), tachypnea (RR >22/minute) and altered mental status (Glasgow coma scale <15 points). Total score ranges between 0 and 3. This score was originally proposed as a screening tool to identify patients with suspected infection outside the intensive care unit (ICU) who are at a high risk for poor outcomes, including hospital mortality in accordance with the new sepsis-3 definition. [Singer M 2016] However, the predictive accuracy of qSOFA might be limited according to recent studies, particularly in the initial evaluation of high-risk patients in the ED. In the original qSOFA study, ED populations were not analyzed separately from the larger study population, and the poor discriminative ability of qSOFA has raised concerns about its role for ED patients requiring early recognition and timely intervention. An extreme variation in a single physiological parameter is not considered to be positive in the qSOFA system. However, as highlighted by Williams et al., one limitation of the new definition is the poor sensitivity of the qSOFA scoring system, which likely excludes its use as a screening tool for early sepsis, the stage in which treatment is most effective. [Williams]

The NLR (neutrophil lymphocyte ratio) is one of the simplest and easily available hematological parameters that can be utilized for subcategorization of patients on severity scale as well as an independent prognostic factor for disease evaluation. Farkas J had stated in his study that several multidisciplinary studies included NLR as prognostic factor, for example: in traumatic brain injury, acute pancreatitis, acute and complicated appendicitis, colorectal malignancy, Head and neck malignancy, intracranial hemorrhage, pulmonary embolism etc. NLR can also be used to assess the severity of sepsis, degree of bacteremia and to differentiate between septic and cardiogenic shock. The values of NLR ratio will be presented in range which is useful to categorize physiological stress. This can also be used as an inflammatory biomarker. [Farkas J] Neutrophil-to-lymphocyte ratio is an easily derived parameter obtained from routine hemogram by dividing absolute neutrophil count to absolute lymphocyte count. The ratio suggests the vascular response against altered hemodynamic milieu in critically ill patients. Several studies reported sensitivity of NLR in prognosis of disease, however its role in early diagnosis of sepsis and septic shock is under investigation.

Suetrong B described in their study that lactate is a metabolite formed during anaerobic glycolysis and is associated with sepsis and tissue hypoxia. Hyperlactatemia and lactic acidosis are common in patients with septic shock and are associated with significant morbidity and mortality. [Suetrong B] As a result, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) has included hyperlactatemia over 2 mmol/L in the revised definition of septic shock. [Suetrong B]

Kraut JA described that lactic acidosis results from the accumulation of lactate and protons in the body fluids and is often associated with poor clinical outcomes. [Kraut JA] According to Rivers E and Jansen TC, lactate is a parameter of global tissue hypoperfusion and is essential in identifying patients with “cryptic” shock who require focused early goal-directed therapy (EGDT). [Rivers E, Jansen TC]

Since sepsis had a complex pathophysiology which include several cellular and molecular response going on simultaneously in an additive manner to flare the response rapidly, looking for an individual biomarker is not going to be much helpful but the combination of several biomarkers may help in a better way. [Biron MB 2015]

The lacunae observed after extensive search in published articles through Google search engine and PubMed database, is lack of any single and or panel of clinical and laboratory tools in spite of discovery of thousands of biomarkers with proven association with sepsis, that could accurately identify sepsis in minimum time and should be rapid, time saving and minimally invasive so that clinicians can start Goal Directed therapy within time to improve patient outcome.

This study is designed to observe the role of qSOFA score, NLR and Lactate in patients with suspected infection, its early diagnostic implication and its correlation with **qSOFA** in predicting early sepsis, mortality and critical care requirements in patients presented to emergency department.

REVIEW OF LITERATURE

Sepsis is a complex, dynamic and resource-demanding clinical entity frequently encountered in critical care settings. Sepsis was first mentioned in Hippocrates' writings and is derived from the Greek word "sepo," which means "I rot." The documented use of term Sepsis at first time was about 2700 years ago found in Homer's poems. [Gyawali B 2019]

The modern definition for sepsis was given by Hugo Schottmuller in 1914 as "sepsis is present if a focus has developed from which pathogenic bacteria, constantly or periodically invade the blood stream in such a way that this causes subjective and objective symptoms". The first consensus definition of sepsis was founded by Roger Bone and his colleagues in SCCM-ACCP conference organized in 1991 "as the presence of both suspected infection and two of the four criteria of the systemic inflammatory response syndrome (SIRS)". [ACCP1991]

Sepsis may have been perceived with a humbler eye a couple of decades ago, but now the scenario has changed. Once easily treatable with antimicrobials, several common microorganisms have camouflaged themselves with a diverse armamentarium of antimicrobial resistance, belittling the available antibiotic arsenal. No longer being a local or regional public health problem, sepsis now demands a global perspective on an urgent basis. What makes the situation even worse in developing countries like India has limitations of resources (drugs, infrastructure and human resources). The high prevalence of HIV/AIDS and delayed referrals pose further challenges to healthcare providers in developing countries.

From past two decades the significant advances in pathobiology of sepsis with better understanding of cellular response, biochemistry, immunology and morphology, changes in circulation and organ function have led to the changes in the definition of sepsis and its progressing events. The term sepsis defined by Roger Bone and his colleagues is known as Sepsis – 1 which leads to the onset of Systemic inflammatory response syndrome (SIRS). The diagnostic criteria for SIRS were defined by presence of > 2 criteria of tachycardia (hear rate > 90 beats/min), tachypnea (respiratory rate > 20 breaths/min), fever or hypothermia (temperature > 38 or < 36^0 C) and leucocytosis, leucopenia or bandemia (WBC > 1200/cmm, < 4000/cmm or bandemia > 10%). With time in 2001, a task force (2001) [Marik PE] expanded the list of diagnostic criteria, resulting in the introduction of Sepsis-2 and defined it as an individual must have at least 2 SIRS criteria and a confirmed or suspected infection. [Bone RC]

The progression of sepsis is further named as severe sepsis and septic shock. Severe sepsis is defined as sepsis complicated by organ dysfunction which could progress to septic shock.

Septic shock is defined as unrecovered hypotension despite adequate fluid replacement in the Surviving Sepsis Campaign (SSC) Guidelines. Sepsis-induced arterial hypotension is defined as a systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure (MAP) < 70 mmHg or a SBP decrease > 40 mmHg or less than two standard deviations below normal for age in the absence of other causes of hypotension. .[Dellinger RP] In 2016, SCCM/ESICM had proposed Sepsis-3 in which sepsis is defined as life threatening organ dysfunction caused by a dysregulated host response to infection.[Singer M 2016]

Patho-physiologically the host immune response to sepsis is characterized by two sequential stages: first is a hyper-inflammatory response and second is compensatory anti-inflammatory response syndrome (CARS). The hyper-inflammatory response is also known as cytokine storm in which two events are going on simultaneously: one is release of proinflammatory cytokines from activated innate immune system to overcome underlying infection and recruitment of members of adaptive immune response to mount an intense immune response. This event is followed by systemic deactivation of immune system and restoration of homeostasis. Lactic acidosis induced acidic milieu depresses the cardiac function and decreases vasopressor response. Roughly 9% of patients with sepsis progress to severe sepsis out of which 3% experience septic shock, accounting for 10% of admissions to ICU. [Singer 2016] Organ failure occurs in 33.6% of the patients with sepsis. Severe sepsis carries estimated 30-50% mortality. 70% of the patients with three or more organ failures die. Those who survive sepsis have been found to have a lower quality of life compared to the general population. [Singer M 2016, Zahorec R 2001, Jiang I 2018, Ljungstrom L 2017, Riche F 2015, Salciocioli]

Diagnosis of sepsis include clinical and laboratory examination either individually or in combination in the form of criteria, scores, bundle or panel. The most important clinical parameters that are altered severely in sepsis are RR, HR, Blood pressure, temperature and altered sensorium. The criteria for diagnosis and prognosis of sepsis evolved are SIRS, Severe sepsis Campaign, Sepsis bundle, APACHE II, SOFA, GCS, qSOFA and many more. Thousands of molecular markers are studied in sepsis among which White blood cell count, Absolute neutrophil count, Absolute lymphocyte count,

Neutrophil:Lymphocyte ratio, Platelet count, Platelet: Lymphocyte ratio, lactate, cytokines, chemokines, acute phase reactants, PCT, CRP, blood culture and many more. However, in past two decades there is no consensus developed yet an accurate diagnostic and prognostic marker for sepsis.

Studies describe significance of SOFA and qSOFA in evaluating the prognosis in sepsis and its comparison with other severity scores like **SIRS**. Patients who fulfill SOFA score have a predicted mortality of ≥10%. However, the complexity of calculation of score, the lack of requisite data for many patients and concerns that it may result in late identification relative to other methods raise the possibility that its use according to the Sepsis-3 method may prove impractical in clinical practice. Recognizing these practical limitations, the 2016 SCCM/ESICM task force described a simplified method termed "quick SOFA" to facilitate easier identification of patients potentially at risk of dying from sepsis. [Annexure II] This score is a modified version of the SOFA known as qSOFA that consists of only three components each allocated one point. It was found that qSOFA is a good prognostic marker for mortality and multi organ failure in septic patients but is not a good diagnostic marker for sepsis. [Singer M2015]

Williams et al. highlighted the poor sensitivity of the qSOFA scoring system in diagnosis of Sepsis-3, which likely excludes its use as a screening tool for early sepsis, the stage in which treatment is most effective. [Williams] Rodriguez et al showed that qSOFA is equal to or better than SIRS in predicting the critical illness in septic patients admitted to ED. [Rodriguez et al] Data from New Zealand intensive care society showed that interventions like intubation, sedation and mechanical ventilation

can interfere with the validity and accuracy of qSOFA score among critically ill patients. [Raith EP et al, Peirovifar A et al]. Though APACHE II, SOFA and SIRS criteria were followed widely since long time for prognosis of sepsis but due to limitations of time constraint, data availability and complexity of scoring these criteria are not adequate in early phases of sepsis where qSOFA will be the clinical diagnostic criteria of choice.

Among biochemical markers for diagnosis of sepsis most studied one is serum lactate level. Lactate is important source of energy, particularly during starvation. It also contributes to acidic environment by converting to lactic acid. Next, lactate is converted to bicarbonate and becomes a main source of alkalemia under normal conditions. Lactate of 1,400–1,500 mmol/L per day is formed from the reduction of pyruvate which is generated largely by anaerobic glycolysis. In tissue hypoxia, lactate is overproduced by increased anaerobic glycolysis. Lactate clearance typically occurs in the liver (60%), followed by the kidney (30%) and to a lesser extent by other organs (heart and skeletal muscle). [Jeppesen JB]

The mortality rate of septic patients with hyperlactatemia (≥4 mmol/L) is 30%, with hypotension alone is 36.7% and both hypotension and hyperlactatemia is 46.1%. [Levy MM] Lee SM et al reported significantly higher acute hospital mortality in septic patients with hyperlactatemia than with lower serum lactate level. [Lee SM] Blood lactate levels can be easily and quickly determined hence these have been used as a surrogate of tissue hypoperfusion in critically ill patients admitted to ED or to ICU. Indeed, increased blood lactate levels have been used to identify critically ill patients at high risk of death even before the development of hemodynamic instability,

i.e., cryptic shock, as well as to trigger resuscitation. [Rady MY] Therefore, the early detection of septic shock based on a new definition is very important because early management of infection can reverse lactic acidosis and shock status.

Among hematological markers, recently NLR become a diagnostic tool of choice because of rapid and easy availability of test and high sensitivity and specificity in early diagnosis of sepsis. It is a ratio of absolute neutrophil to lymphocyte count which can be easily calculated from WBC differential counts. It ranges between 00 to 100 and a normal NLR is roughly falls within 1 – 3. The rise in NLR will indicate about underlying hypoxia any type of physiological or pathological stress. Zahorec R observed that NLR increases rapidly following acute physiologic stress (<6 hours). This prompt response time may make NLR a better reflection of acute stress than other hematological parameters. Interpretation of NLR depends on clinical context. Critically ill patients may have NLR > 9 which sometimes reach upto 100. NLR interpretation is considerably influenced in clinical context. For example, inflammatory disorders may tend to elevate NLR more than non-inflammatory disorders. Thus, a patient with sepsis and an NLR of 15 might not be tremendously ill, whereas a patient with a pulmonary embolism and an NLR of 15 is more worrisome. Jiang J et al had mentioned in their article that there are literatures flooded with studies using the NLR for everything from sepsis to cancer to restless leg syndrome but none of the studies used NLR along with qSOFA as a tool for early predictor of sepsis and to assess the disease severity. [Jiang J]

Farkas Jet al described studies that evaluated the ability of NLR to detect bacteremia, mostly in heterogeneous populations of patients presenting to ED however its

performance is poor. Meta-analysis shows that with a cutoff of ~10, NLR has a sensitivity of 72% and specificity of 60%. [Farkas J]

NLR has proven more useful in comparison to low or high white blood cell count (WBC) alone in sepsis when the two are directly compared. Ultimately, NLR may be a logical replacement for the WBC. In some situations, NLR is competitive with more expensive biomarkers (e.g., procalcitonin, lactate). Within specific clinical contexts (e.g., pancreatitis, pulmonary embolism), NLR may have surprisingly good prognostic value.

Studies show that NLR had similar performance compared to lactate or Procalcitonin. The sensitivity of NLR in relation to cut off value was also studied in various researches and it was found that a cutoff of 3 had higher sensitivity for sepsis than any other test (95%). Thus, a normal NLR (<3) argues against sepsis. NLR of > 10 support a diagnosis of sepsis. Intermediate values (3-10) fall within a grey zone.

Though NLR is a novel marker that evolved in last few years as a diagnostic and prognostic marker to differentiate between inflammatory versus non-inflammatory critical illness, between infectious and non-infectious critical diseases and indicator of poor prognosis with rise in its trend in time. This marker is also not exempted from few limitations.

Jiang J described the limitation of NLR indication in sepsis in their study as performance of the NLR for bacteremia among undifferentiated patients is limited due to the heterogeneous nature of this population. Many patients have severe physiologic stress (with elevated NLR) without bacteremia. Alternatively, some patients with bacteremia tolerate this surprisingly well and aren't very ill. In short, it's unrealistic to

expect NLR to perform well in this context. This isn't a failure of the test itself, but rather it represents a failure to apply the test appropriately. [Jiang I]

Limitations in NLR interpretation is multifactorial. Farkas et al had mentioned in detail about them. These factors include administration of exogenous steroid that increase margination of peripheral pool of neutrophils and hence increase the NLR in absence of bacteremia. Patients having active hematological disorders like leukemia, cytotoxic chemotherapy or Granulocyte colony stimulating factor (G-CSF) may affect white blood cell count and its differentiation leading to abnormally high or low NLR. In addition to that patients with advanced AIDS and chronic lymphopenia might be expected to have a higher baseline NLR. Ljungstrom et al evaluated the performance of several markers among a population of 1,572 patients admitted to ED with a clinical suspicion of sepsis. [Ljungstrom et al]

As discussed above in detail, no single test is found to be effective and better than other when early and accurate diagnosis as well as prognosis of sepsis is concerned. Several studies are performed to describe relationship of NLR with timing of death. Rich'e F in a recent study showed a reversed NLR evolution according to the timing of death, whereas Salciccioli J. D. suggested no association between level of NLR and sepsis related mortality. [Rich'e F, Salciccioli J D] Consequently, the clinical usefulness of NLR in patients with sepsis is therefore still a matter of ongoing controversy and this question deserves further investigation.

Liu X et al were stated in their study the NLR levels of the patients with positive blood culture were significantly higher than the ones with negative blood culture (22.65

(IQR, 12.60 to 36.93) versus 14.66 (8.15 to 25.62), *P* = 0.000). Although the median length of stay in the hospital was similar between survivors and non-survivors (*P* = 0.468), the median length of stay in the ICU was significantly longer in non-survivors (*P* =0.041). [Liu X] The NLR measured at the time of admission to ICU was associated with 28-day mortality and correlated well with disease severity, according to APACHE II score. NLR was able to accurately stratify patients in terms of short-term mortality. These findings remained robust after adjusting for several potential covariates, suggesting that increased NLR was independently associated with unfavorable outcome in patients with sepsis. The strength of the NLR is the possibility of implementing this parameter simply by using already available biomarkers (neutrophil count and lymphocyte count). Therefore, this ratio is easy to integrate in clinical practice and is cost effective.

Younan D et al compared in their study between demographic data, injury mechanism and severity (ISS) score, NLR at admission and at 24 and 48 hours and organ failure data. They describe their result for NLR patterns during the first 48 hours by dividing it into two trajectories identified by applying factor and cluster analysis to longitudinal measures. Statistical analysis shows 36% patients with Trajectory 1 had a mean NLR at admission of 3.6, which increased to 14.7 at 48 hours. 64% patients in Trajectory 2 had a mean NLR at admission of 8.5 which decreased to 6.6 at 48 hours. Mean NLR was different between the two groups at all three time points. Models adjusted for age, gender and ISS showed that trajectory 1 were more likely to have organ failure and degree of AKI than in Trajectory 2. In all cases, the estimated associations were higher among men vs. women, and all were significant among men, but not in women. They

conclude that Trauma patients with an increasing NLR trajectory over the first 48 hours had increased risk, number and severity of organ failures. [Younan D]

Soulaiman et al had studied NLR among poly trauma patients and stated that in contrast to the widespread activation of neutrophils post-injury, the fall in total lymphocyte levels usually occurs in response to multiple traumas. The prognostic value of NLR had already studied in the diagnosis of familial Mediterranean fever, in acute appendicitis in relation to leucocytosis and estimated in non-traumatic disorders with higher sensitivity. Hence NLR can potentially be used as an early indicator of inflammatory homeostasis derailment in patients with tissue injury. They concluded that elevated NLR during the first 24 h of admission (day 1) has high predictive power for overall survival during the first 30 days after trauma, but it was not independent of other factors. [Soulaiman et al]

Connor H and Foucher CD, studied lactate level and its sources in human body. Lactate is produced normally by skin, red cells, brain tissue, muscles and gastrointestinal tract. Lungs can produce lactate during acute lung injury without tissue hypoxia, and leukocytes generate lactate during phagocytosis or when activated in sepsis. Normally lactate is produced in excess by about 20 mmol/kg/day, which enters the bloodstream. [Connor H, Foucher CD]

Lactate is metabolized by liver and kidneys either by direct oxidation or as a source of glucose. According to Levy B lactate can be transformed into oxaloacetate or alanine via pyruvate pathway or can be utilized directly by periportal hepatocytes (60%) to produce glycogen and glucose (neoglycogenesis and neoglucogenesis; Cori cycle). 30% of lactate metabolism is done by kidneys in which the cortex classically acting as

metabolizer by neoglucogenesis and medulla as a producer of lactate. [Levy B] described the role of lactate in inflammation as it can modulate inflammation and promote immune tolerance. [Garcia-Alvarez M, Sun S] Sun S and Nasi A observed that lactate increases cellular production of anti-inflammatory cytokines such as interleukin-10. [Sun S and Nasi A] On the other hand Errea A and Husain Z stated that it reduces the activities of pro-inflammatory cytokines such as IL-12, macrophages, natural killer cells, and tumor necrosis factors. [Errea A, Husain Z] According to Mahnensmith RL and Malo ME in acute tissue ischemia, ischemia-induced lactic acid formation is an important cellular response which is activated by the plasma membrane sodium proton exchanges. [Mahnensmith RL, Malo ME] Sun S and Regli L stated that it increases intracellular sodium, and it leads to calcium overload via calcium-sodium exchange and inducing cell death. [Sun S and Regli L] According to Sikes PJ and Wu D in the setting of sepsis related lactic acidosis, animals which pretreated with sodium-proton exchanger blockers develop less hemodynamic instability and better survival compared with non-treated control groups.[Sikes PJ, Wu D] Suetrong B and Herbertson MJ in their studies mentioned that in sepsis and septic shock state, this critical oxygen extraction ratio is decreased to 50% or less so that lactic acid formation increases at oxygen deliveries that would normally be sufficient to meet the aerobic oxygen demand. [Suetrong B, Herbertson MJ] According to Suetrong B and Garcia-Alvarez M, microcirculatory dysfunction, which impairs oxygen delivery to the tissues, and mitochondrial dysfunction, which impairs oxygen utility, occur in patients with sepsis so that, even in an adequate oxygenation, anaerobic metabolism occurs and pyruvate is shunted toward lactate

production. [Suetrong B,Garcia-Alvarez M] Suetrong B and Levraut J found that reduced lactate clearance enhanced hyperlactatemia. In sepsis patients whose vital signs were stable, hyperlactatemia might be induced by the dysfunction of hepatic lactate clearance, which is primarily due to pyruvate dehydrogenase (PDH) inhibition. [Suetrong B, Levraut J] Levy B stated that in patients with sepsis and low-flow state, chronic liver disease further compromises lactate clearance. PDH converts pyruvate into acetyl-CoA, allowing pyruvate to enter the mitochondria. PDH activity was decreased in patients with septic muscle and is restored by dichloroacetate thus decreases hyperlactatemia in patients with sepsis. [LevyB] Foucher CD stated that regardless of the source, increased lactate levels have been associated with worse outcomes. Lactic acidosis can cause a reduction of cardiac contractility and vascular hypo-responsiveness to vasopressors through various mechanisms. It is a precipitator of mortality and contributes to a worsening of underlying comorbidities.

Casserly B in their studies stated that in normotensive patients with sepsis, a lactate concentration more than 4 mmol/L was found to be independently correlated with higher mortality and therefore needs urgent recognition and proper resuscitation. [Casserly B] However, Tang Y et al stated that patients with septic shock with intermediate concentrations of lactate (2–4 mmol/L) have poorer prognosis than those with normal lactate concentration. Moreover, in the severity score, lactate weighted scoring system discriminated mortality significantly than others such as sequential organ failure assessment score. [Tang Y] According to Singer M et al the Sepsis-3 task force recommended that the monitoring of lactate should not be used as a guide to evaluate patient’s therapeutic response or should not be used as an indicator of illness

severity. They recognized that serum lactate measurements are commonly, but not universally, available, especially in developing countries. [Singer M] Lactate weighted scoring system discriminate mortality significantly than others such as SOFA score and APACHE II among the severity score. Early diagnosis and prompt institution of antibiotic therapy form the cornerstone of sepsis management. There is an urgent need for tools to assess the severity of sepsis for early identification and prognostication of sick patients who warrant aggressive treatment and monitoring. This study is proposed to identify role of qSOFA score, serum lactate level and NLR in diagnosis of sepsis in early phase and their association with each other.

AIMS AND OBJECTIVES OF THE STUDY

PRIMARY OBJECTIVE

To evaluate the role of levels of NLR, lactate and qSOFA score as a predictor of sepsis in patients presenting to ED with suspected infection.

SECONDARY OBJECTIVE

- To evaluate levels of NLR, lactate and qSOFA score in predicting mortality in sepsis patients.
- To determine cut off levels for NLR and lactate values among patients with sepsis related mortality.
- To compare NLR and lactate levels with qSOFA and qSOFA alone in early prediction of sepsis in patients presented to ED with suspected infection.

MATERIALS AND METHODS

Study site:

The study was conducted in patients presenting with clinical symptoms and signs of sepsis as per Sepsis – 3 definitions, admitted to ED of BLDE (DU) Shri BM. Patil Medical College Hospital and Research Centre, Vijayapura, for the duration of November 2021 to September 2022.

Study design:

It was a single center prospective observational study.

Study population:

347 adult (≥18 years old) medical patients admitted for more than 24 hours with the clinical diagnosis of severe sepsis/septic shock as per Sepsis -3 definition at the time of admission and fulfilling all inclusion criteria were included in the study.

Sample size: Sample size was calculated by using the formula for observational studies.

$SS = \frac{(Za)^2 PQ}{D^2}$, where

Za = Z alpha, taken as 1.96 with 95% confidence interval

P = prevalence of disease severity in population which is considered to be 25% based on previous studies

Q (100-P) = the difference of P value from100

D = precision of estimate, calculated as 20% of P value, since P value for this study is 25, hence value for D is 5.

After the calculation based on the above-mentioned formula, we require 300 cases to

be enrolled for this study.

Inclusion Criteria:

1. All patients of age more than 18 years presenting with suspected infection to the Emergency Department.
2. All adult patients willing to provide informed consent for recruitment in the study.
3. Documented source of infection anywhere, either clinically or by laboratory/radiological investigation.

Exclusion Criteria:

1. Pregnancy
2. Patients on immunosuppressive drugs or chemotherapy.
3. Patients with neuro-psychiatric illness.
4. Patients already on antibiotic therapy.
5. Medical history of hematological disorders such as leukemia, myelodysplastic syndrome, neoplastic metastases to the marrow etc.
6. Chronically immunosuppressed (defined as immunosuppression for solid organ transplantation, post-splenectomy, receiving ≥ 10 mg/d prednisolone or equivalent for ≥ 30 days, treatment with other immunosuppressive agents, or neutropenia [neutrophils $\leq 1.0\times10^9$/L]

METHODOLOGY

We recruited patients admitted to the ED according to our Institutional protocol for severe sepsis and septic shock resuscitation, prepared on the basis of Sepsis – 3 guidelines. Clinical examination of all recruited patients was done and vitals were recorded. Careful external examination for presence of any kind of localized lesions responsible for sepsis was done. qSOFA scoring was performed. All the samples for investigation were collected within 1 hour of patient admission and transported to the respective laboratory as per protocol. Peripheral venous blood was drawn in EDTA vacutainer under aseptic condition for Complete blood count. Hemogram was performed by fully automated 5-part hematology analyzer (Model XN1000, Sysmex, Japan). Peripheral arterial blood was drawn in a heparinized syringe under aseptic condition for Arterial blood gas (ABG) and lactate level analysis performed by fully automated ABG analyzer (Model ABL 80 FLEX, Radiometer, Japan) . Blood or other body fluid or focal lesion swabs if any were collected for microbiological investigation –culture and sensitivity. Patients were sub grouped clinically into severe sepsis and septic shock based on GCS status, SBP level and serum lactate level. First of all, patients were stabilized according to ABCD management guidelines followed by which fluid resuscitation initiated with administering crystalloids at the rate of 20 – 30 ml/kg and empirical antibiotics. Other supportive measures were taken immediately as per the department treatment protocol. All invasive procedures were performed as per requirement and lines were secured. Goal-directed therapy was applied to patients with severe sepsis associated with arterial lactate levels at least 3.0 mmol/L or those who remained hypotensive (SBP < 90 mmHg or MAP < 65 mmHg) despite fluid

resuscitation with administration of vasopressor agents, sodium bicarbonates etc. The following therapeutic goals were targeted during the first 6 hrs. of resuscitation: SBP $\geq$ 90 mm Hg, MAP at least 65 mmHg, improvement in qSOFA score, decrease in temperature, central venous oxygen saturation ($ScvO_2$) at least 70%, and diuresis at least 0.5 mL/kg/h.

The following data were collected and recorded: demographic characteristics, admission diagnosis, quick Sepsis-related Organ Failure Assessment (SOFA) score, site of infection, hemodynamic and chemical parameters, administered treatments (fluids, vasopressors, steroids, and antibiotics) during the first 24 hrs. of ED admission, clinical improvement in vitals, progression or regression in organ function status and mortality at day 1.

STATISTICAL ANALYSIS

All the data were collected by using a pretested proforma meeting the objectives of the study. Detailed history, physical examination and necessary investigations had undertaken. The purpose of the study was explained to the patient in their own language and informed consent obtained. All the clinical and laboratory data were gathered and entered in Microsoft Excel sheet.

Categorical variables were expressed as absolute numbers and in relative frequencies (%) whereas numerical variables were presented as Mean ± SD and continuous variables as Mean with confidence interval at 95% level (CI 95%).

Binary variables were compared with chi-square test or with Fisher exact test when appropriate. Comparison of numerical variables between groups will be found using unpaired t-test/ Anova test.

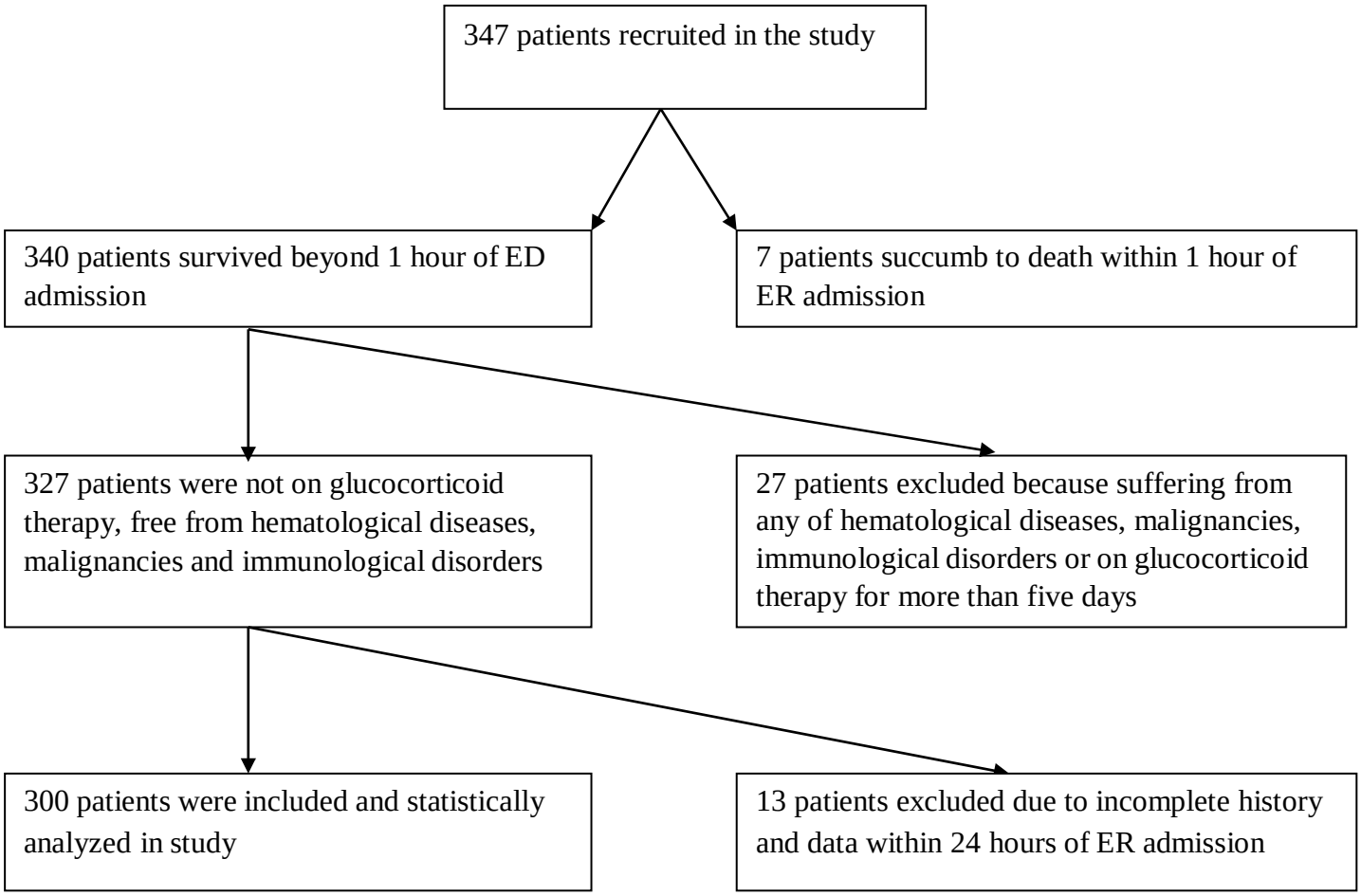
A receiver-operating characteristic (ROC) curve was constructed to assess the best blood lactate level and NLR cutoff related to mortality at day 1. Subsequently, patients were dichotomized according to the lactate and NLR cutoff separately chosen by ROC curve analysis. We calculated sensitivity and specificity value for the cutoff values of Lactate and NLR. We also constructed ROC curves to test the ability of initial lactate levels, NLR and qSOFA score to predict mortality at day 1in the subgroup of patients of ED admission.

RESULTS

347 patients admitted to ED who fulfilled the criteria for severe sepsis or septic shock based on Sepsis-3 are enrolled and prospectively evaluated in the study period from NOV 2021 to SEP 2022. 47 patients are excluded from the study because of different reasons like death within 1 hour of admission (7), presence of hematological diseases, malignancies, immunological disorders, on glucocorticoid therapy for more than five days (27) and incomplete history and data due to loss to follow up (13). [Figure 1]

FLOW DIAGRAM OF PATIENT RECRUITMENT

FIGURE 1.



RESULT

Total 300 patients were included in the study and data were gathered and analyzed. We analyzed the frequency of categorical variables like age, gender, survivors, non-survivors, qSOFA score with disease outcome, culture positive or negative, patients with sepsis with or without vasopressors etc. in Mean ± SD and percentage. Continuous variables we selected in our study were lactate and NLR levels in microbiologically confirmed cases of sepsis, their sensitivity and specificity in early diagnosis, finding a cut off value for these variables in relation with clinical outcome in sepsis and correlation of them with qSOFA score in combination and alone.

The Mean age of study population is 49.54 years (range19 - 98 years) with most of them are ≥ 39 years. The gender distribution is as186 males (62.00%) and 114 females (38.00%). This study shows higher prevalence of sepsis among middle aged male patients than younger or elderly population. We sub grouped patients into four groups based on the age range with difference of twenty years in first three groups and fourth one with patients having age > 79 years. We observed that there is no significant difference between age distribution among males and females in group one i.e. early age with sepsis but group two, three and four shows males are affected more with sepsis in comparison to females. [Table 1, Figure 2&3]

TABLE 1: DISTRIBUTION OF CASES BY AGE AND GENDER

Age Range (years)	Male (%)	Female (%)	Total cases	Percentage
19 – 38	48 (25.81%)	47 (41.23%)	95	31.67%
39 – 58	71 (38.17%)	25 (21.93%)	96	32.00%
59 – 78	59 (31.72%)	32 (28.07%)	91	30.33%
>79	8 (04.30%)	10 (08.77%)	18	06.00%
Total	186 (62.00%)	114 (38.00%)	300	100.00%

FIGURE 2: DISTRIBUTION OF CASES BY AGE AND GENDER

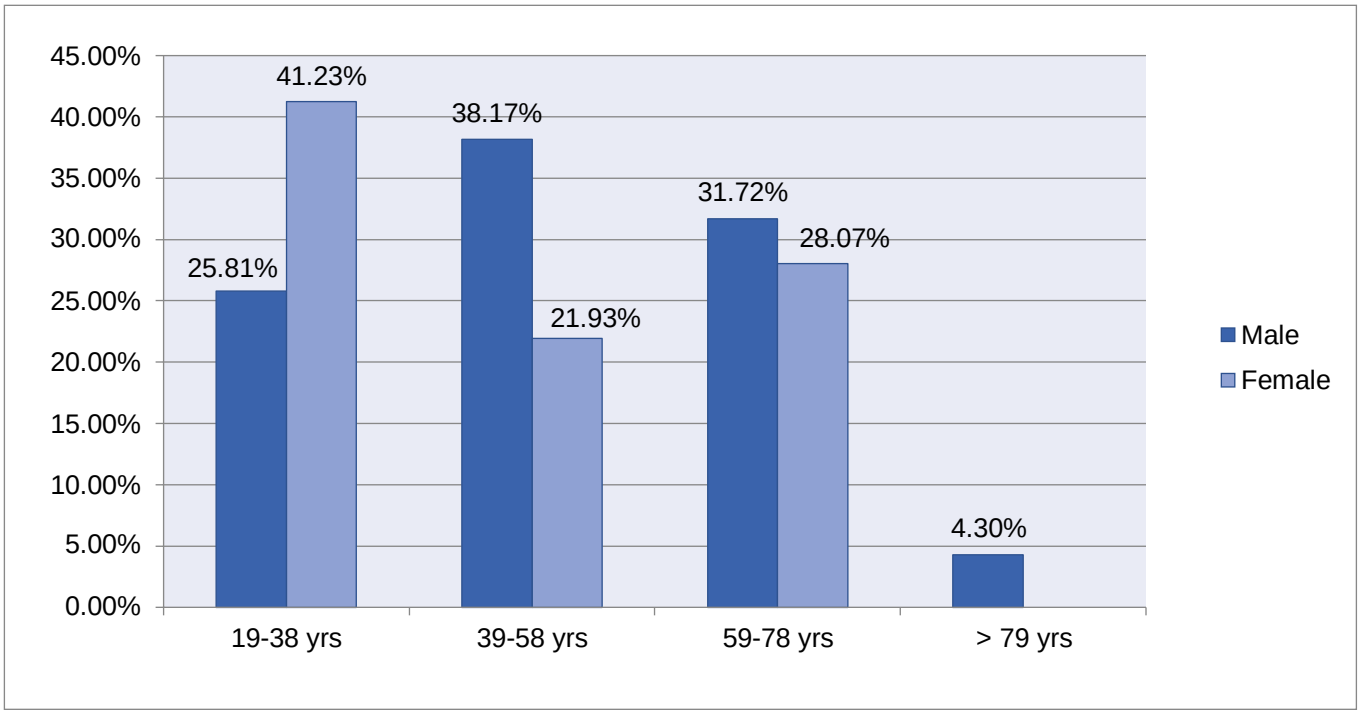
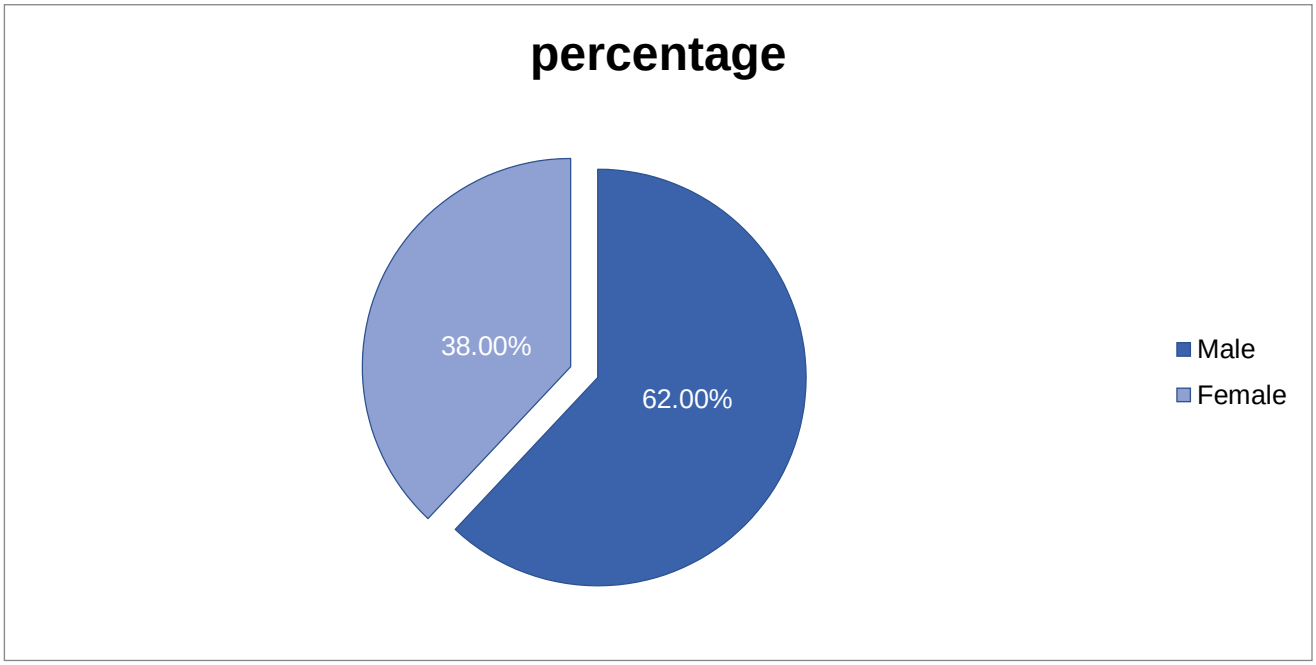


FIGURE 3: OVERALL GENDER DISTRIBUTION OF CASES



RESULT

The usual patient stabilization and observation time in ED in our Institute is 12 to 24 hours after which patients are shifted to respective departments. Patients are managed according to Surviving Sepsis Guideline. We assessed clinical condition and survival of patients at 24 hours post admission. Patients are subdivided into two groups, Group I i.e., Survivor (S) and Group II i.e., Nonsurvivor (NS) based upon their survival after 24 hours of admission. The age and gender distribution among both groups show high prevalence in middle age group i.e., 39 to 58 years with male predominance (Male: Female ratio 10:1). Mean age in Survivor and Non-survivor group is 49.18 $\pm$ 18.05 years (CI 95% 46.99 – 51.37) and 52.11 $\pm$ 19.13 years (CI 95% 45.73 – 58.49) observed in this study which indicates favorable survival outcome among younger age than extremes of age. [Table 2, Figure 4&5]

TABLE 2. DISTRIBUTION OF AGE AND GENDER AMONG SURVIVOR AND NONSURVIVOR GROUPS

Variables			Group I (S)	Group II (NS)
Number of patients: N (%)			263 (87.67%)	37 (12.33%)
Age group: N (%)	19 – 38 years	M	43 (16.35%)	5 (13.51%)
		F	42 (15.95%)	5 (13.51%)
	39 – 58 years	M	63 (23.95%)	10 (27.03%)
		F	25 (9.51%)	1 (2.70%)
	59 – 78 years	M	50 (19.01%)	7 (18.92%)
		F	30 (11.41%)	3 (8.11%)
	> 79 years	M	6 (2.28%)	3 (8.11%)
		F	4 (1.52%)	3 (8.11%)

FIGURE 4: DIAGRAMMATIC REPRESENTATION OF AGE DISTRIBUTION BETWEEN SURVIVOR AND NON-SURVIVOR GROUPS

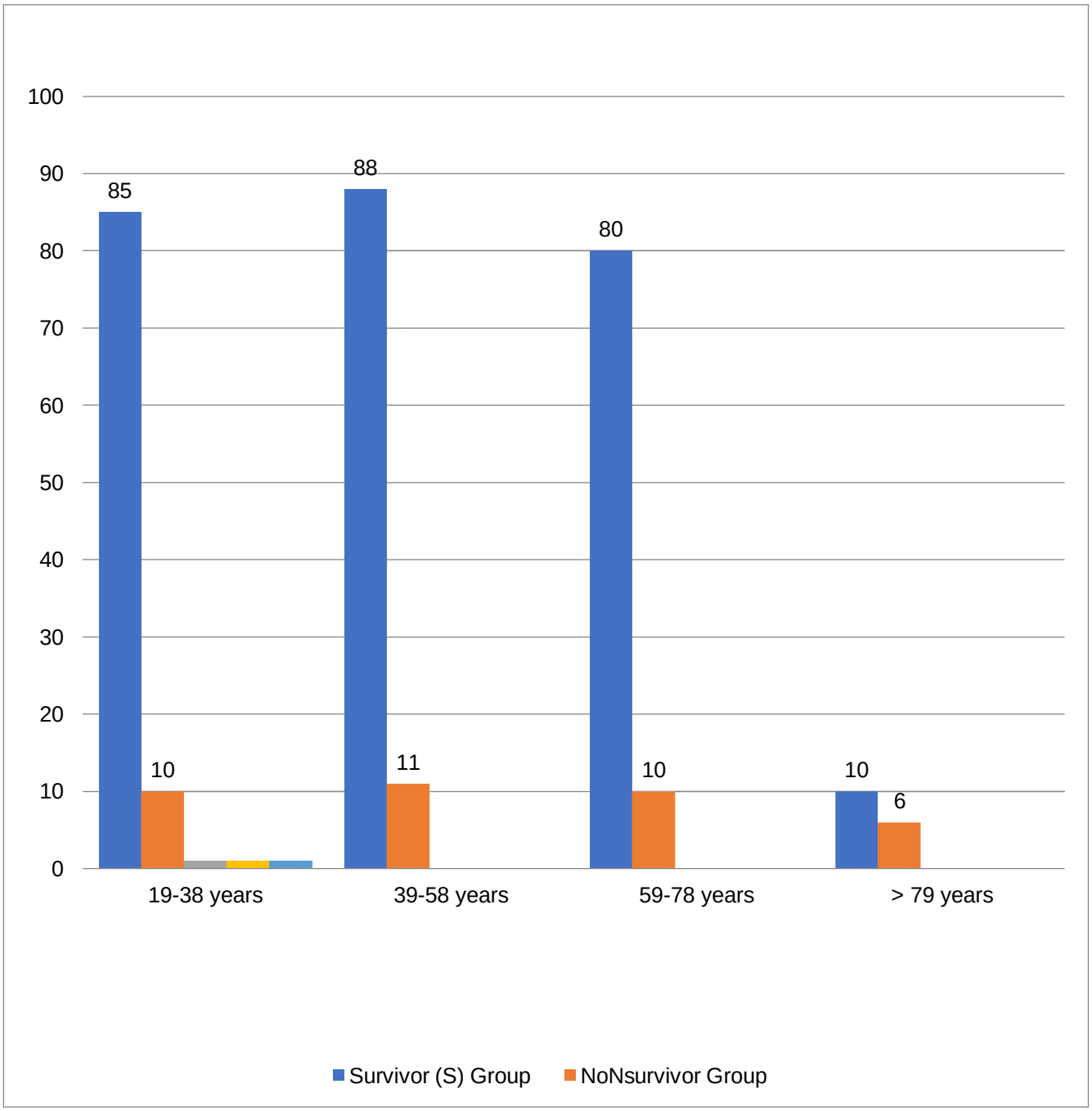
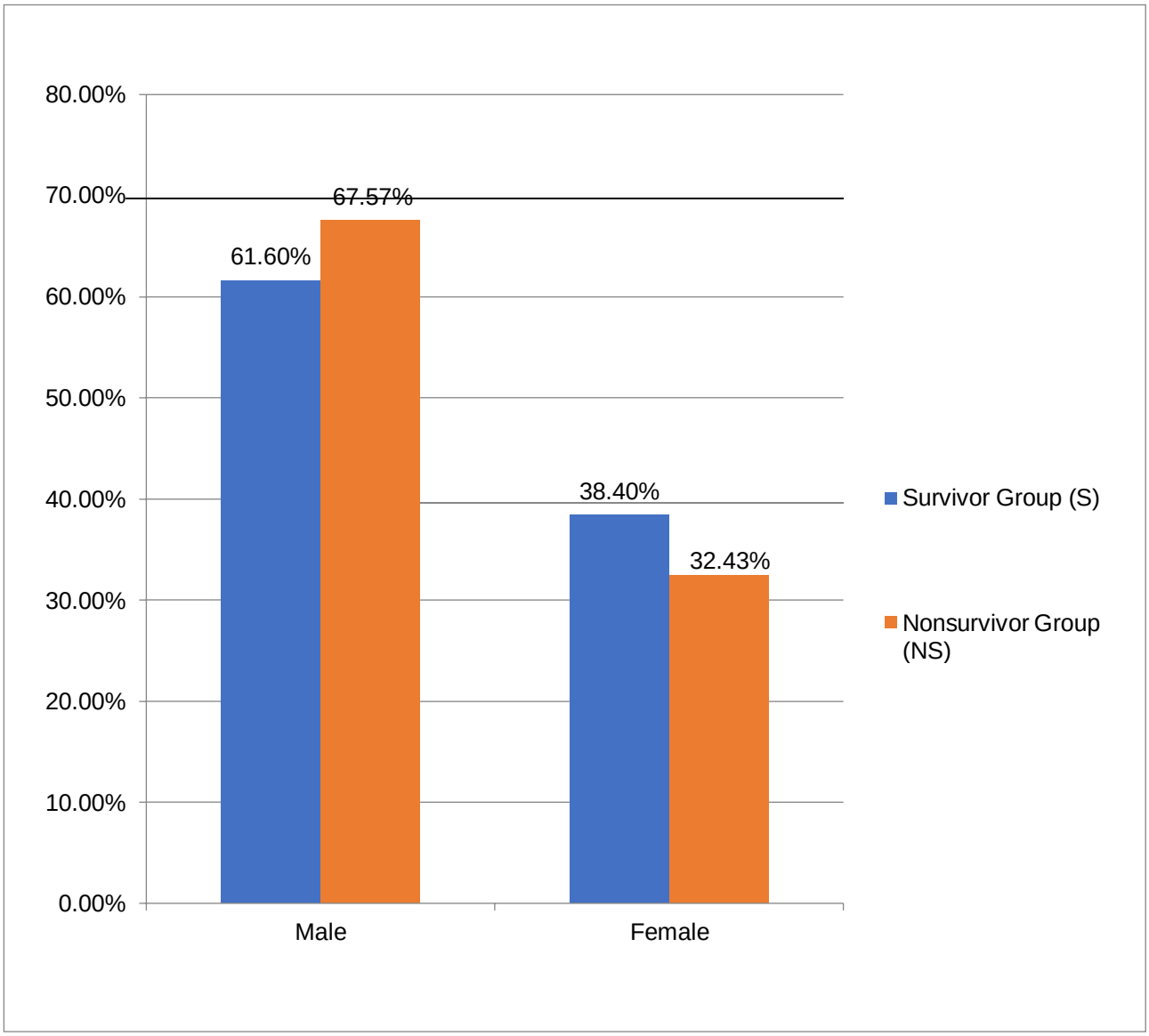


FIGURE 5: DIAGRAMMATIC REPRESENTATION OF GENDER DISTRIBUTION BETWEEN SURVIVOR AND NON-SURVIVOR GROUPS



RESULT

Patients with qSOFA score of 2 and 3 are selected for recruitment in the study and compared among (S) and (NS) groups. Patients with lower score of 2 had better survival than score 3. Among patients with score of 3, 61.05% are in survivor group in comparison to 38.95% in non-survivor group. qSOFA with score 2 shows fair agreement among Survivor group with male predominance whereas qSOFA score 3 shows no statistical significance among survivors and nonsurvivors when categorical variable, gender is compared with chi-square test. The chi-square statistic was 1.31 without Yates correction and 0.86 with Yates correction. All the patients irrespective of Survivor or Nonsurvivor group had received fluid resuscitation for underlying hypotension and observed for correction of SBP > 90 mm Hg or MAP > 65 mm Hg within first hour of admission. Those patients who failed to reach the targeted SBP and or MAP are further managed with vasopressor. Out of 300 patients, 164 (54.67%) required vasopressor in addition to fluid therapy for stabilization of SBP and/or MAP and rest 136 (45.33%) were responded well to fluid therapy and other supportive treatment. Correlation of qSOFA score with gender in both (S) and (NS) groups shows male predominance. Vasopressive agents are administered to all the patients having qSOFA score of 3 (survivors and nonsurvivors) and non-responders to fluid therapy within 10 minutes of administration among those with qSOFA score 2. 77.47% patients survive after administration of vasopressive agents (127/164) with qSOFA score 2 and 3, P <0.003.[Table 3, Figure 6&7]

TABLE 3. DISTRIBUTION OF GENDER AMONG qSOFA CASES REQUIRING VASOPRESSOR

Gender	Patients on vasopressor with qSOFA score 2	Patients on vasopressor with qSOFA score 3
Male: n (%)	66 (73.33%)	49 (66.22%)
Female: n (%)	24 (26.67%)	25 (33.78%)
Total: n (%)	90 (100%)	74 (100%)

FIGURE 6. HISTOGRAM SHOWING THE DIFFERENCE IN qSOFA SCORE AT ADMISSION BETWEEN SURVIVORS (S) AND NON-SURVIVORS (NS)

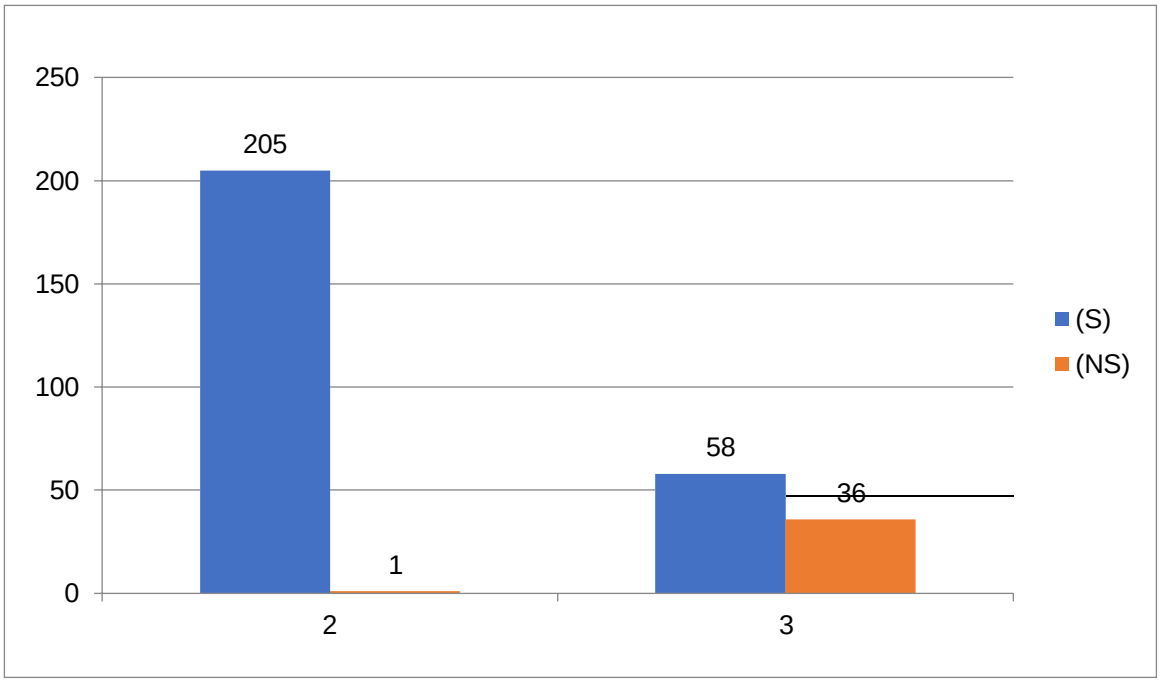
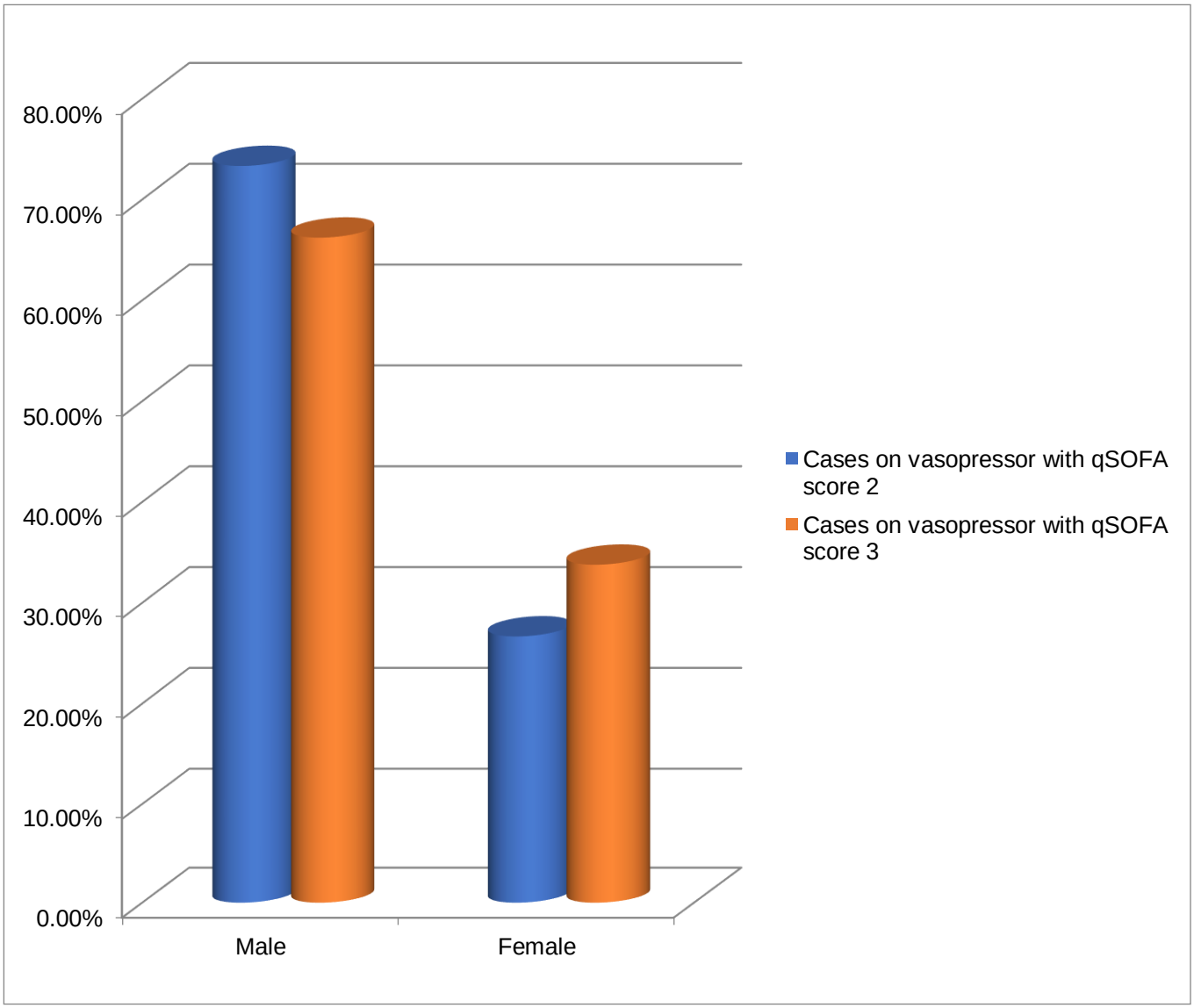


FIGURE 7. HISTOGRAM SHOWING GENDER DISTRIBUTION AMONG qSOFA CASES REQUIRING VASOPRESSOR



RESULT

Hemogram of patients shows leucocytosis with neutrophilia predominantly followed by lymphopenia and leucopenia. Neutrophilia shows left shift upto band forms (bandemia > 10%), presence of cytoplasmic azurophilic granules, toxic granules and vacuoles and occasionally apoptotic cells. The average distribution of total leucocyte count (TLC), absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) in this study was 770 to 80480, Mean 16411.29 $\pm$ 10175.6 (CI 95% 15255.16-17567.43), 97.23 to 77421.76, Mean 14043.3 $\pm$ 9563.32 (CI 95% 12956.71-15129.85) and 11.59 to 31297.41, Mean 1715.45 $\pm$ 2790.89 (CI 95% 1398.35 – 2032.54) respectively. The hemogram analysis reveals higher TLC (35.14%), ANC (59.45%) and NLR (64.86%) and low ALC (67.57%) among males of non-survivor group in comparison to those in survivor group. Among survivor group, males have higher ANC (49.05%) and NLR (56.65%) and low ALC (60.08%) than females. The mean value for NLR and lactate in this study is reported as 15.47 $\pm$ 15.07 (CI 95% 13.76 – 17.19) and 3.27 $\pm$ 3.02 (CI 95% 2.93 – 3.62) respectively. The maximum value observed for NLR and lactate was 87.9 and 27 respectively in this study. [Table 4 &5]

TABLE 4. DISTRIBUTION OF HEMOGRAM AMONG SURVIVOR AND NON – SURVIVOR GROUPS

Subgroup	Sex	TLC (per µl)		ANC (per µl)		ALC (per µl)		NLR	
		>15000	< 15000	> 7000	< 7000	> 4000	< 4000	> 3	< 3
Nonsurvivor (NS)	M	35.14%	32.43%	59.45%	8.11%	00.00%	67.57%	64.86%	2.71%
	F	21.62%	10.81%	27.03%	5.41%	5.41%	27.02%	24.33%	8.10%
Survivor (S)	M	24.72%	36.88%	49.05%	12.55%	1.52%	60.08%	56.65%	4.94%
	F	18.63%	19.77%	28.90%	9.50%	3.80%	34.60%	31.94%	6.46%

Table 5: COMPARISON OF DEMOGRAPHIC & CLINICAL DATA BETWEEN SURVIVORS AND NON-SURVIVORS

Variables		Survivor (n=263/300)		Non survivors (n=37/300)
		Sex	N (%)	N (%)
Age N (%)	19 – 38 years	M	43 (16.35%)	5 (13.51%)
		F	42 (15.95%)	5 (13.51%)
	39 – 58 years	M	63 (23.95%)	10 (27.03%)
		F	25 (9.51%)	1 (2.70%)
	59 – 78 years	M	50 (19.01%)	7 (18.92%)
		F	30 (11.41%)	3 (8.11%)
	> 79 years	M	6 (2.28%)	3 (8.11%)
		F	4 (1.52%)	3 (8.11%)
qSOFA Score	2	M	125 (47.53%)	00 (00.00%)
		F	80 (30.42%)	00 (00.00%)
	3	M	34 (12.93%)	26 (70.27%)
		F	24 (9.12%)	11 (29.73%)
TLC	< 15000	M	95 (36.12%)	13 (35.14%)
		F	53 (20.15%)	3 (8.11%)
	> 15000	M	63 (23.95%)	13 (35.14%)
		F	52 (19.78%)	8 (21.61%)
PMN	< 7000	M	12 (4.56%)	2 (5.40%)
		F	16 (6.08%)	00 (00.00%)
	> 7000	M	143 (54.37%)	25 (67.57%)
		F	92 (34.99%)	10 (27.03%)
LYMPHO	< 4000	M	158 (60.08%)	25 (67.57%)
		F	91 (34.60%)	10 (27.02%)
	> 4000	M	4 (1.52%)	00 (00.00%)

		F	10 (3.80%)	2 (5.41%)
NLR	< 3	M	13(4.94%)	1 (2.71%)
		F	17 (6.46%)	3 (8.10%)
	> 3	M	149 (56.65%)	24 (64.86%)
		F	84 (31.94%)	9 (24.33%)
LACTATE	< 4	M	139 (52.85%)	0 (00.00%)
		F	88 (33.46%)	0 (00.00%)
	> 4	M	22 (8.37%)	26 (70.27%)
		F	14 (5.32%)	11 (29.73%)

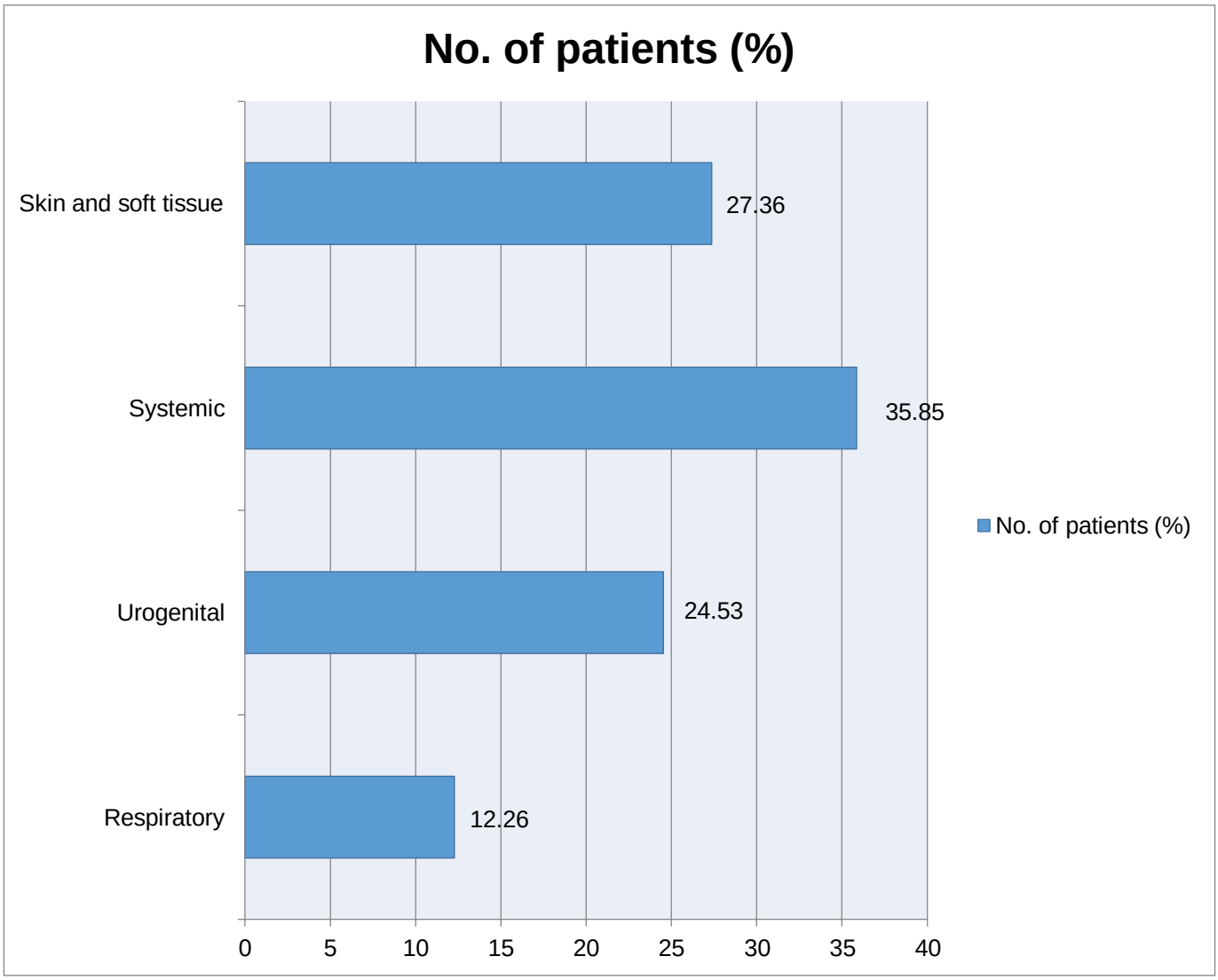
RESULT

The site of infection is also analyzed in this study. Out of 300 cases only 106 (35.33%) are culture positive for pathogenic organisms. Systemic and cutaneous and soft tissue sites of infection show higher frequency among both the groups (S & NS). The gender distribution shows male predominance (69.81%) in systemic and cutaneous and soft tissue infection among both the groups (S & NS). This may happen due to availability of incomplete history regarding previous intake of antibiotics by patients for their underlying illness about which they are not aware at the time of providing history about drug intake. [Table 6, Figure 8]

Table 6: DISTRIBUTION OF CASES BY SITE OF SEPSIS

Site of sepsis	**Frequency distribution among patients: N (%)**	**Survivor group: N (%)**		**Non survivor group: N (%)**	
		M	F	M	F
Respiratory	13(12.26%)	7(6.61%)	5(4.72%)	1(0.94%)	0(00.00%)
Urogenital Tract	26(24.53%)	11(10.38%)	10(9.43%)	3(2.83%)	2(1.88%)
Skin And Soft Tissue	29(27.36%)	20(18.88%)	8(7.55%)	1(0.94%)	0(00.00%)
Systemic	38(35.85%)	25(23.58%)	8(7.55%)	4(3.77%)	1(0.94%)
Total	106	63(59.45%)	31(29.25%)	9(8.48%)	3(2.82%)

FIGURE8. HISTOGRAM SHOWING FREQUENCY DISTRIBUTION OF SITES OF INFECTION AMONG SURVIVOR AND NON-SURVIVOR GROUPS

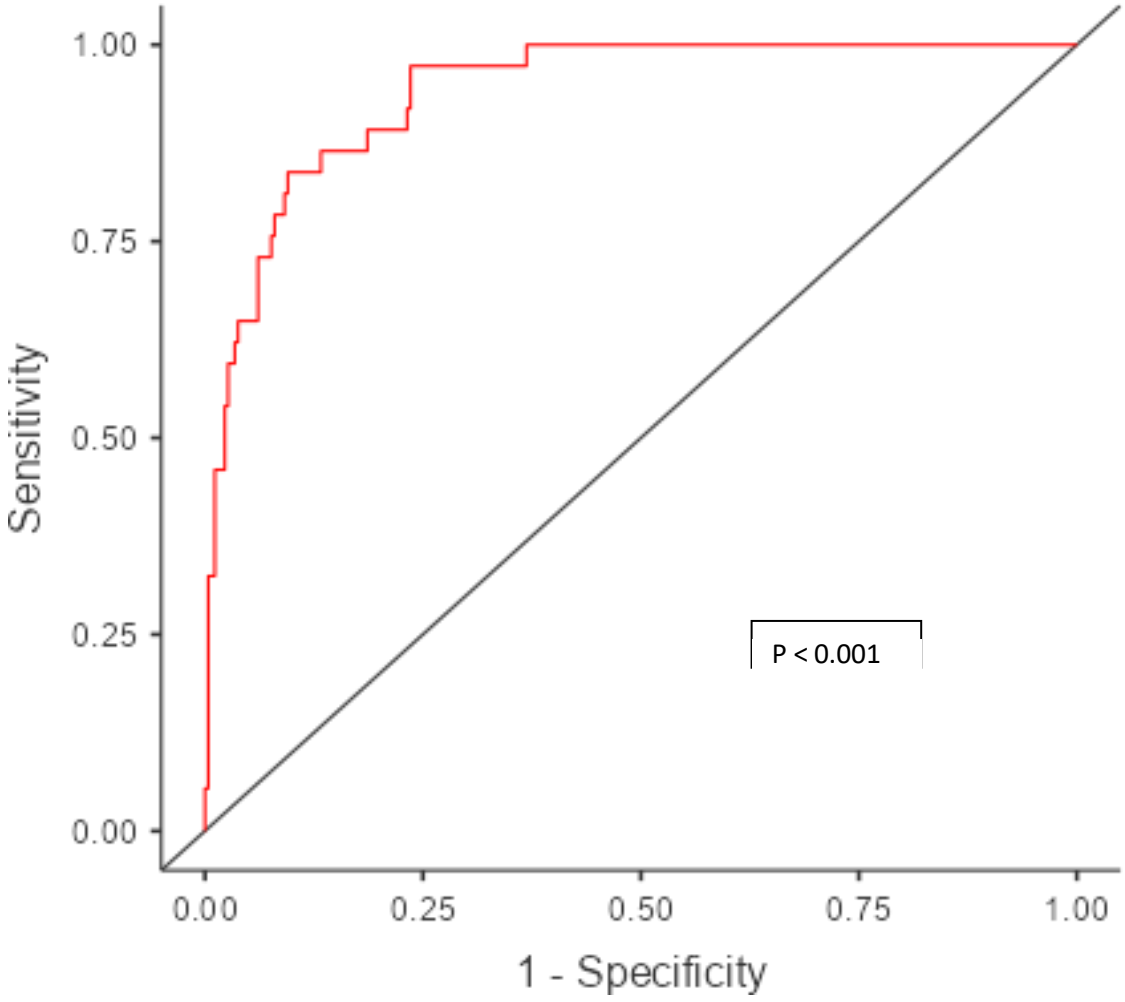


RESULT

A Receiver-operating characteristic (ROC) curve was constructed to assess the best blood lactate level and NLR cutoff related to mortality at day 1. Subsequently, patients were dichotomized according to the lactate and NLR cutoff separately chosen by ROC curve analysis. We calculated sensitivity and specificity value for the cutoff values of Lactate and NLR. We also constructed ROC curves to test the ability of initial lactate levels, NLR and qSOFA score to predict mortality at day 1in the subgroup of patients of ED admission. Highest sensitivity (50.26) and specificity (54.21) observed for serum lactate level at 2.5 mmol/L value hence cut off point was rounded off to 3 in this study for ease of calculation. NLR level shows poor sensitivity but higher specificity with value 45.2. Hence, we difficult to derive a cut off value for NLR value in this study.

Receiver operating characteristic curve analysis was performed to assess the diagnostic accuracy for predicting disease outcome at day 1 and the area under the curve (AUC) was calculated. The area under curve (AUC) for NLR shows good predictive value with accuracy for diagnosis of sepsis as an independent marker. [Figure 9]

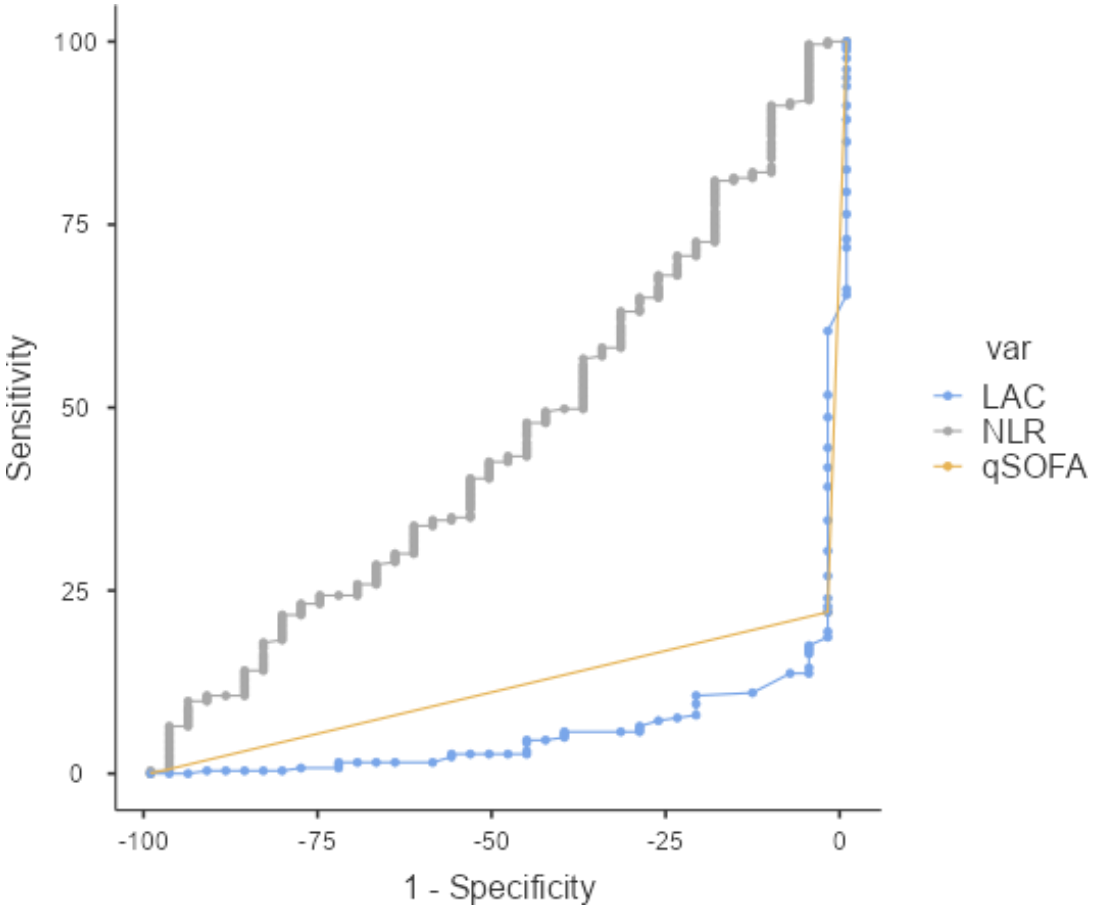
FIGURE 9. ROC CURVE FOR NLR AS A DIAGNOSTIC MARKER FOR EARLY SEPSIS



RESULT

The ROC curve for qSOFA score, NLR and serum lactate shows poor sensitivity but good specificity. The combined use of qSOFA score, serum lactate and NLR to detect sepsis at the earliest is analyzed by using ROC curve. [Figure 10]

FIGURE 10. ROC CURVE OF qSOFA, NLR AND LACTATE AS DIAGNOSTIC MARKER FOR EARLY SEPSIS



RESULT

Correlation between qSOFA score, serum lactate level and NLR with culture reports was analyzed by using paired Student T – Test that shows significant association between them ($p < 0.001$).

Level of TLC and serum lactate as predictor of disease outcome (S & NS groups) was analyzed by logistic regression that shows significant association with disease outcome with Odds Ratio 1.000 and 1.989 ($p = 0.032$, $p<0.001$) respectively. NLR was found to be no longer effective in predicting disease outcome, OR 0.997 ($p=0.841$).

Correlation matrix for qSOFA score with serum lactate level ($p<0.001$) and with NLR ($p=0.009$) was significant however NLR with serum lactate was found to be non-significant.

We did univariate analysis and compared qSOFA score, NLR and lactate levels between survivors and non-survivors. Outcome shows significant association of qSOFA score ($p<0.001$) and serum lactate levels however NLR is a poor indicator for outcome ($p=0.773$). All these three variables are found to be independent predictor of disease diagnosis and outcome as well.

This study had analyzed demographic data, patient outcome, role of three mostly used markers in sepsis –qSOFA score, serum lactate level and NLR individually and in combination to discover their utility as a diagnostic tool for sepsis in early phase. The result shows good correlation of qSOFA score and serum lactate levels in early diagnosis of sepsis but role of NLR is questionable.

DISCUSSION

Early phase of sepsis needs easy clinical parameters for patient assessment without any assistance and rapid bedside investigations that could assess biochemical and hematological parameters accurately. Several studies had reported qSOFA as a good independent predictor of sepsis and is easy to perform. [Singer M, Marik PE,]

We observed that the incidence of sepsis is higher among middle aged group males and females in our study which is in coherence with Daga MK study. [Daga MK] Kaushik R et al also reported mean age of 30 years among patients with sepsis in their study which is a decade earlier than in our study (49.54 years). [Kaushik R] The median age (50 years) in this study is varied by two decades earlier in comparison to western world. [Filho RR, Chicco D] However this variation in age prevalence is may be due to drastic change in life style, especially dietary habits, in past two decades among Indian population and small sample size in comparison to other studies. The study shows mean age of 52 years among nonsurvivors suggesting risk of mortality increases with senescence. The sepsis related mortality rate was 12.33 % and is correlated well with the studies of Singer M et al. [Singer M] In the present study, the primary outcome, i.e., mortality at day 1, was 12.33% which is similar to be reported in study of Filho R R et al (12.77%). [Filho RR]

Frequency of site-specific sepsis was also analyzed in this study and we observed that bacteremia was the most common site of sepsis (35.85%) meant by presence of pathogen within blood, followed by cutaneous (27.36%) and urogenital infections (24.53%). Filho RR et al reported respiratory tract infection (50.6%) as most common

site followed by urinary tract infection (20.3%) in sepsis patients in their study. This variation may be due to epidemiological and demographic factors.

The primary outcome of this study was to describe role of three most commonly used markers of sepsis independently and in combination.

Most of the studies compared several scores as screening, diagnostic and prognostic tool for sepsis like APACHE II, SOFA score, qSOFA score etc and found that qSOFA score is a good predictor of sepsis in prognostic aspects and with mortality also. The qSOFA score in this study shows poor outcome with score of 3 in comparison to score of 2. Shahsavarinia K et al observed 66.3% sensitivity and 60.6% specificity for qSOFA in detection of sepsis and recommended that qSOFA as a good prognostic marker but not for diagnosis. [Shahsavarinia K] Rhodes A et al had clearly recommended that though qSOFA is a good predictor of mortality, it cannot be used singly for screening and diagnosis of sepsis. This score was not included in the most recent Surviving Sepsis Campaign guidelines 2017 to screen or diagnose sepsis. [Rhodes A] Several other researches had also compared effectiveness of qSOFA with SOFA and found that qSOFA could predict disease outcome more significantly and since it is very easy to perform even in patients with altered mental status and not included any laboratory marker, most of them favor to use it. We correlated qSOFA score with culture report for diagnostic confirmation and found significant relation between the two ($p < 0.001$).

Serum lactate level measurement at the time of ED admission is very important and valuable marker as baseline level it can be used for further monitoring and prognosis of patients. In addition to that since it's a marker of tissue hypoxia and hypoperfusion

the level of this marker will help in definite therapy of hypotension at the earliest with better choice of regimen. The median for serum lactate level among patients with sepsis at the time of admission in ED was 2.4 which is well correlated with that found in study of Filho RR. We observed that serum lactate level at 2.5 mmol/L have highest sensitivity and specificity in diagnosing the disease itself and in prognosis of disease associated mortality. This finding is in coherence with that reported by Filho R R et al. They observed that initial lactate levels above 2.5 mmol/L had a mortality rate 3.2 times higher than patients with initial normal lactate level. [Filho RR] Thus we recommend use of a cut off value of 3mmol/L (rounded off) to be considered for diagnostic purpose. However, serum lactate level is influenced by several factors hence its independent use as screening and diagnostic tool requires further large-scale study with inclusion of all possible factors determining serum lactate level.

Complexity of numerical and morphological presentation of hemogram in sepsis make its interpretation challenging as there is involvement of peripheral and central hematological cellular pool well regulated by various chemical mediators. Since multiple factors are activated simultaneously in sepsis like external or internal pathogens, acute inflammatory response releasing chemical mediators at a higher rate and hypoxia induced diffuse tissue injury. Hence, we found TLC and ANC as a good predictor of disease outcome in sepsis but are poorly correlated with culture reports. This may happen due to heterogenous response of myeloid cells towards pathogen in population.

TLC was well correlated with diagnosis of sepsis in early phase with mean of 16.41 $\pm$ 10.17(95% CI – 11.56) in this study. Similar values were reported by Liu X et al

(mean 16.07 ± 6.63). [Liu X et al] Both leucocytosis and leucopenia were associated with poor prognosis. The differential count of white blood cells shows markedly high ANC and markedly low ALC. Thus, we found higher value for NLR among cases having TLC within normal range. NLR plays an important role in disease prognosis in such situation. This may be due to various underlying factors. Most important among them are early stage of effective bone marrow suppression by underlying disease with superadded sepsis mediated increase in chemical mediators (IL-6), medication, fluid imbalance etc. TLC, ANC, ALC and NLR were studied individually and in combination, as diagnostic marker for sepsis by several researchers. Kaushik R et al found NLR at a value of ≥ 3.3 with higher sensitivity and specificity (87.5% & 90% respectively) and recommended it as a diagnostic marker in early phase of sepsis. Our study shows poor outcome with NLR of > 10 among patients in early phase of sepsis. ALC shows lymphopenia of moderate to severe degree in sepsis patients at early phase which correlates well with the study of Kaushik R. et al and Jilma et al. Jilma et al observed persistently high ANC among patients with sepsis and concluded that these patients have very poor outcome due to persistent lymphocytopenia. [KaushikR, Jilma] The median value for NLR was 10.58 in this study similar to be reported by Ahmed M.A.M.S. et al (median NLR value 8.6). They concluded that NLR at day 1 of admission is a good prognostic marker for mortality but haven't commented upon its use as diagnostic tool. NLR with culture reports show positive correlation ($p<0.001$) similar to the study of Liu X et al who reported higher NLR in positive blood culture cases ($p=0.000$). [Liu X]

qSOFA score (2 & 3), hyperlactatemia (≥ 3 mmol/L) and NLR (> 3) shows significant

role in prediction of disease severity and mortality at day 1 of ED admission when studied individually. We observed correlation between individual and combined use of these markers in diagnosis and prognosis of sepsis.

Combined use of qSOFA score and serum lactate is studied vigorously till now and proven prognostic markers independently and in combination both among sepsis patients. There was positive correlation between qSOFA and serum lactate level with culture reports and disease outcome in present study and is in coherence with the study of Filho RR et al and Daga MK. Daga MK termed LqSOFA when it is used in combination with lactate level of > 2 mmol/L. They also recommended these markers as prognostic tool. [Filho RR, Daga MK] qSOFA and NLR shows positive correlation to predict disease outcome ($p=0.009$) similar to reported by Li Y et al in their study. They concluded significantly higher sensitivity and specificity of qSOFA and NLR as a prognostic marker for prediction of mortality when used in combination. Though they haven't studied diagnostic role of these two markers. [Li Y]

The combined use of qSOFA score with serum lactate level and NLR for diagnosis of sepsis in early phase is noninferior than their individual use. This study observed that though all these three markers are very good predictor of mortality at day 1 of ED admission they are not showing superior effect in comparison to their individual utilization. However, we recommend that multiple factors are regulating the clinical state of patients presenting in ED, further study at large scale will be needed with inclusion of these possible factors to understand the effectiveness of utility of these markers in sepsis.

STRENGTHS & LIMITATIONS

This study had a prospective design. All patients were managed under similar settings with uniform institutional management protocol based on surviving sepsis guidelines. The patients were first categorized into severe sepsis or septic shock followed by immediate initiation of sepsis bundle of management. We attempted to follow all the instructions according to Institutional guidelines and stick to patient selection criteria as per study design protocol. The clinical outcome in this study shows satisfactory results that may be due to early and rapid clinical assessment and diagnosis which is further supported by easy to perform and early to avail serum lactate and NLR values.

However, the present study is not exempted from limitations. Since the markers we selected are more common than the other one, a large-scale study including thousands of populations is needed to validate the results we observed. We are limited in time period for study population recruitment (12 months) hence unable to recruit patients on a large scale. We observed poor correlation of these markers with culture reports. This may have limitations in difficulty to obtain proper history as patients came in critically ill condition thus not in a state of providing detailed history regarding previous drug intake. Since this was a single Centre study conducted in a tertiary care institution, results may not be generalized to the entire population. Hemogram shows extremes of values that are not well correlated with lactate levels, qSOFA and culture reports. This may happen as hematological response is time dependent and respond heterogeneously with multifactorial events occurring simultaneously among patients with sepsis. In addition to this there are several limitations related to logistics and at technical grounds were affected the result of our study.

CONCLUSIONS

In this prospective observational study, 300 patients admitted to ED with symptoms and signs suggestive of sepsis, qSOFA score, serum lactate level and NLR were assessed within two hours of admission with the aim to utilize them as early predictor of sepsis. We conclude that these markers had significant role in prognosis of disease outcome in the form of day1 mortality independently and in combination but to diagnose sepsis in early phase when culture reports are not available, they show heterogenous behavior. qSOFA with serum hyperlactatemia (> 3 mmol/L) is a good predictor in diagnosing early phase of sepsis without waiting for culture reports but NLR is a poor predictor for the same. Hence, we recommend that further research is needed to find a new gold standard to replace culture report so that we could utilize the golden period within time in sepsis patients to save their life.

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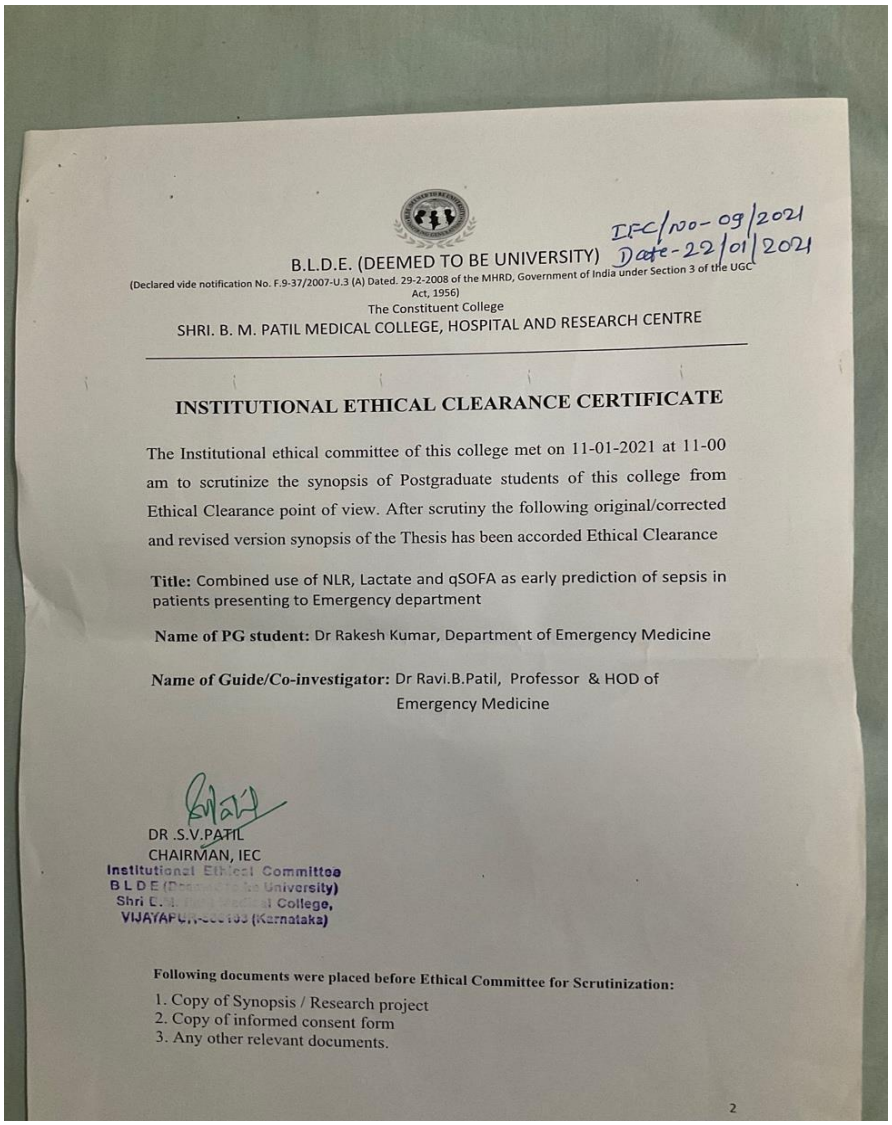
ANNEXURE I

ETHICAL COMMITTEE CERTIFICATE



IEC/No-09/2021
Date-22/01/2021

B.L.D.E. (DEEMED TO BE UNIVERSITY)
(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)
The Constituent College
SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Institutional ethical committee of this college met on 11-01-2021 at 11-00 am to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: Combined use of NLR, Lactate and qSOFA as early prediction of sepsis in patients presenting to Emergency department

Name of PG student: Dr Rakesh Kumar, Department of Emergency Medicine

Name of Guide/Co-investigator: Dr Ravi.B.Patil, Professor & HOD of Emergency Medicine

DR .S.V.PATIL
CHAIRMAN, IEC
Institutional Ethical Committee
B L D E (Deemed to be University)
Shri B. M. Patil Medical College,
VIJAYAPURA-586103 (Karnataka)

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

2

ANNEXURE II

INFORMED CONSENT FORM

BLDE (DEEMED TO BE UNIVERSITY) SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR KARNATAKA-586103

TITLE OF THE PROJECT –Combined use of NLR, Lactate and qSOFA as early prediction of sepsis in patients presenting to Emergency department.

PRINCIPAL INVESTIGATOR - Dr. RAKESH KUMAR

P.G. GUIDE NAME –DR. RAVI B PATIL MS (GENERAL SURGERY)

PROFESSOR AND HOD, DEPARTMENT OF EMERGENCY MEDICINE

All aspects of this consent form are explained to the patient in the language understood by him/her.

I) INFORMED PART

1) PURPOSE OF RESEARCH: I have been informed about this study. I have also been given a free choice of participation in this study.

2) PROCEDURE: I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study.

3) RISK AND DISCOMFORTS: I understand that I may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of

my condition and the procedure of this study is not expected to exaggerate these feelings that are associated with the usual course of treatment.

4) BENEFITS: I understand that my participation in this study will help to patient's survival and better outcome.

5) CONFIDENTIALITY: I understand that the medical information produced by this study will become a part of Hospital records and will be subject to the confidentiality and privacy regulation. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by code number. The code-key connecting name to numbers will be kept in a separate location. If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand that I may see the photographs and videotapes and hear the audiotapes before giving this permission.

6) REQUEST FOR MORE INFORMATION: I understand that I may ask more questions about the study at any time. Dr. RAKESH KUMAR is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. If during the study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

7) REFUSAL OR WITHDRAWAL OF PARTICIPATION: I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that Dr. RAKESH KUMAR may terminate my participation in the study after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician or physical therapist, if this is appropriate

8) INJURY STATEMENT: I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study I am not waiving any of my legal rights.

I have explained to_____the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Dr. RAKESH KUMAR Date (Investigator)

II) STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. RAKESH KUMAR has explained to me the purpose of research, the study procedures that I will undergo, and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate as a subject in this research project.

_____ _____

Participant / Guardian Date

_____ _____

Witness to signature Date

ANNEXURE III

BLDE (Deemed to be) UNIVERSITY, SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA KARNATAKA

Combined use of NLR, Lactate and qSOFA as easily prediction in patients presenting to Emergency department

Name: CASE NO:

Age: IP NO:

Sex: DOA:

Religion: DOD:

Occupation: Residence:

Phone No:

Presenting complaints with duration:

- **Past history**

Treatment History:

General Physical Examination

Vitals

PR: BP: RR:

Temp:

QUICK SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

qSOFA (Quick SOFA) Criteria	Points
Respiratory rate ≥22/min	1
Change in mental status (GCS < 15)	1
Systolic blood pressure ≤100 mmHg	1
Total Score	0 - 3

INVESTIGATIONS

Complete Blood Count

- Total Count Cells/cmm
- Differential counts
- Neutrophils % Lymphocytes % Eosinophils % Monocytes % and their absolute values
- HB gm%
- Platelets lakhs/cmm

BIOCHEMISTRY

- Serum Lactate

MICROBIOLOGY

- Blood culture

FINAL DIAGONOSIS

P. G. GUIDE: **DR. RAVI B PATIL**

M.S (GENERAL SURGERY)

PROFESSOR AND HOD

DEPARTMENT OF EMERGENCY MEDICINE

B.L.D.E (DEEMED TO BE) UNIVERSITY

SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL &

RESEARCH CENTER

VIJAYAPUR, KARNATAKA

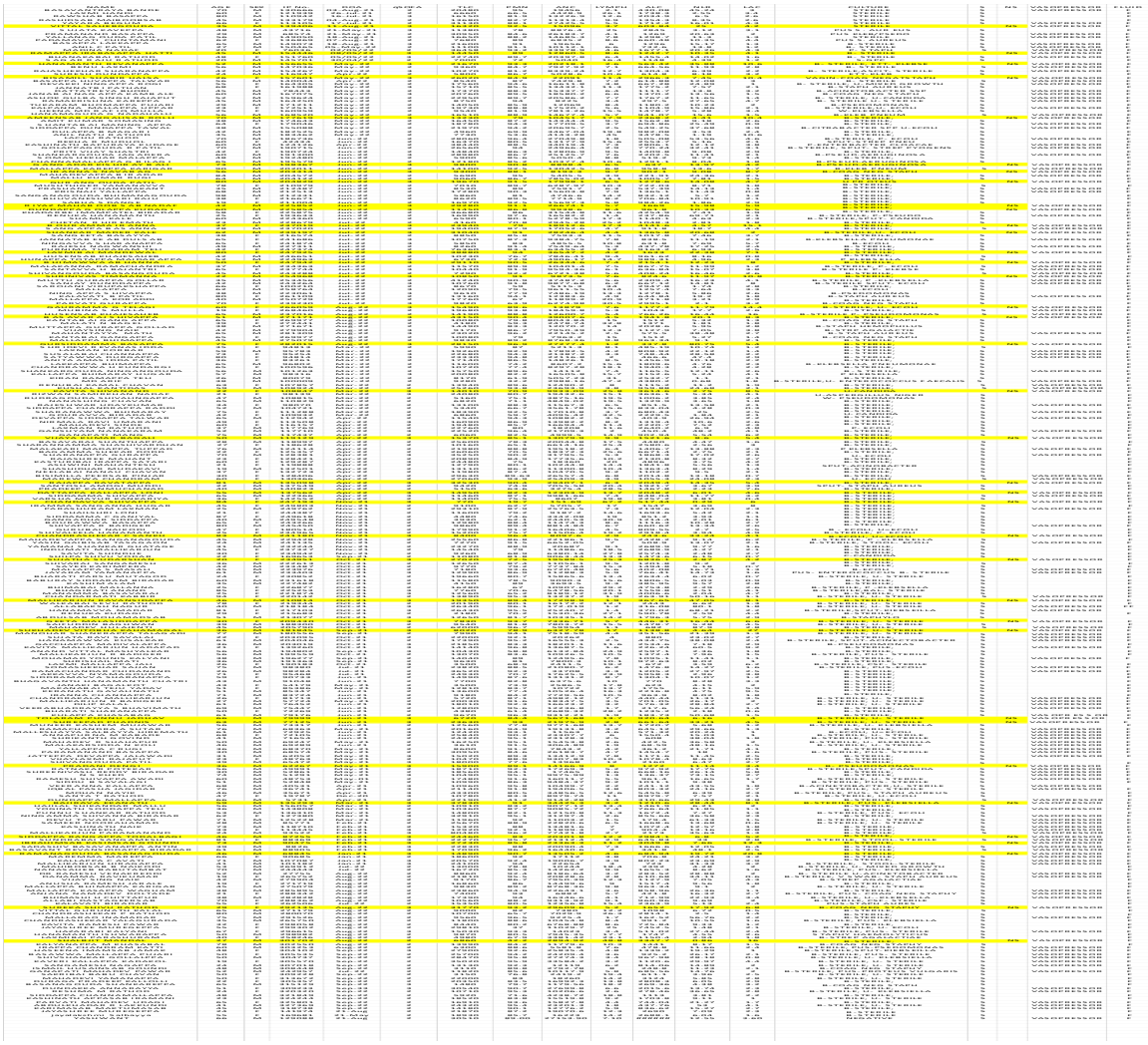
ANNEXURE IV

FORMULA FOR CALCULATION OF NLR:

$$NLR = \frac{\text{Absolute neutrophil Count}}{\text{Absolute lymphocyte Count}}$$

ANNEXURE V

PATIENT MASTER CHART



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