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THE PROGNOSTIC VALUE OF NEUTROPHIL TO LYMPHOCYTE RATIO IN PATIENTS WITH SEPSIS AND SEPTIC SHOCK IN MEDICAL INTENSIVE CARE UNIT OF 108 CENTRAL MILITARY HOSPITAL

By

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THESIS

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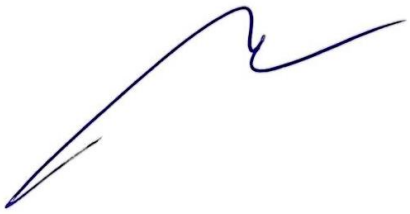

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DECLARATION OF AUTHORSHIP

I am Nguyen Van Viet Thang, 1st cohort of Internal Medicine residents of College of Health Sciences, VinUniversity, hereby declare that:

1. This is my thesis. This thesis was conducted by me under the direct supervision of Doctor Pham Dang Hai.
2. This study has never been published in any journals inside or outside of Vietnam.
3. All the data in this study was collected by me. The data are correct, honest, and objective.
4. The process of conducting this study followed all the regulations stated by VinUniversity and 108 Central Military Hospital.

I will take all responsibilities regarding my thesis.

Hanoi, January 14th, 2024

Signature

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LIST OF ACRONYMS

AKI	:	Acute kidney injury
APACHE	:	Acute physiology and chronic health evaluation
AUC	:	Area under the curve
CKD	:	Chronic kidney disease
COPD	:	Chronic obstructive pulmonary disease
ICU	:	Intensive care unit
MAP	:	Mean arterial pressure
mNUTRIC	:	Modified nutrition risk in the critically ill
NLR	:	Neutrophil to lymphocyte ratio
ROC	:	Receiver operating characteristic
SAPS	:	Simplified acute physiology score
SIRS	:	Systemic inflammatory response syndrome
SOFA	:	Sequential organ failure assessment
TNFα	:	Tumor necrosis factor α

ABSTRACT

➢ **BACKGROUND:**

Sepsis is a serious condition with high mortality. Prompt stratification and treatment are required to decrease its' morbidity and mortality. Neutrophil to lymphocyte ratio (NLR) has been found to have reasonable prognostic value for sepsis mortality. This study aims to evaluate NLR as a prognostic tool for in-hospital mortality in patients with sepsis and septic shock.

➢ **METHOD:**

The study was designed as a single-center retrospective cohort in the Medical Intensive Care Unit of 108 Central Military Hospital from January 2021 to December 2022. A total of 141 cases of newly diagnosed sepsis or septic shock were included. In-hospital mortality was the primary outcome.

➢ **RESULTS:**

The overall mortality was 31.9%. NLR on day 3 was significantly higher in patients with septic shock diagnosis, patients with AKI, and patients who required CRRT. NLR was significantly higher in non-survivors on both day 1 and day 3. NLR had an AUC of 0.68 with a 95% CI of 0.60 – 0.76 in predicting in-hospital mortality. NLR has similar predictive value in predicting in-hospital mortality with SOFA, APACHE II, SAPS II, and mNUTRIC. The best cut-off for NLR was 22.9 with a sensitivity of 51.1% and a specificity of 81.25%. Higher NLR was independent predictors for in-hospital mortality.

➢ **CONCLUSION:**

NLR was an independent predictor of in-hospital mortality and had significant predictive value for poor outcomes in patients with sepsis.

STUDY BACKGROUND

Infectious diseases are common all over the world. In many cases of infection, the body response becomes dysregulated and causes damage to the host itself. These patients presented with different clinical manifestations, and their outcomes also varied significantly. The dysregulation in host response to infection is termed sepsis. Sepsis is a clinical syndrome that can lead to multiple organ failure and death. Sepsis is different from infection by its nature and its severity. As a result, identifying the progression from infection to sepsis is important to guide prompt treatment. Sepsis and septic shock are considered medical emergencies that require prompt diagnosis and treatment because of its' high mortality rate. The incidence of sepsis and septic shock varies among studies. A population-based study in the United States found the incidence of septic shock was 79 cases per 100,000 in 2009. It also reported the overall mortality rate of septic shock is 31.4%.[1]

There is currently no specific guideline on sepsis prognosis. The most commonly used tools for sepsis prognosis are the SOFA and APACHE II scoring systems. SOFA score has reasonable value in predicting mortality with an area under the curve (AUC) of 0.88 with a cut-off of ≥ 7.[1] A study on APACHE II and APACHE III showed an AUC of 0.80 and 0.83, respectively, for predicting sepsis mortality.[2] SOFA is quite simple; however, it still requires arterial blood gas, which may not be available in resource-limited areas. Obtaining these scoring systems takes time. Moreover, suppose we want to use these scoring systems as a follow-up to disease progression after treatment. In that case, we will need extensive testing, which is costly and not feasible in resource-limited areas. Second, even though these systems have proven that higher scores correlate to sepsis mortality and can be used to predict mortality in sepsis, their sensitivity and specificity vary among researchers. The heterogeneity of sepsis and septic shock can partly explain this. Finally, due partly to sepsis' complexity and dynamic nature, there is no gold standard for diagnosis and no proven single tool that can be used to prognosticate sepsis mortality. That is why current researchers continuously work on finding new biomarkers or scoring systems for sepsis prognosis.

Neutrophil to lymphocyte ratio (NLR) is a marker that has been recently studied for mortality prediction. A meta-analysis published in 2020, including 14 studies and 11,564 patients, showed an association between high NLR and poor prognosis in sepsis patients. They found a hazard ratio of 1.75 (95% CI, 1.56 – 1.97, $p<0.01$) between non-survivors and survivors with no significant heterogeneity.[3] NLR's value in sepsis comes from the fact that neutrophil is elevated in an infection state while lymphocyte count is reduced though apoptosis during a hyperinflammatory state like sepsis.[4]

Vietnam is a developing country. Many regions have limited access to important lab tests for sepsis prognosis. NLR is an easy and cheap tool with significant value in sepsis prognosis. Currently, there is no study validating NLR in Vietnamese. We decided to conduct this study to:

1. Describe the Neutrophil-to-lymphocyte ratio changes in patients with sepsis or septic shock.
2. Evaluate the correlation of Neutrophil-to-lymphocyte ratio with some prognostic factors of severity and mortality in patients with sepsis and septic shock.

CHAPTER 1. INTRODUCTION

1.1 SEPSIS AND SEPTIC SHOCK

1.1.1 Definition of sepsis and septic shock

From the third international consensus definitions for sepsis and septic shock, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[5] It is quite different from the original definition of sepsis in the 1992 ACCP-SCCM consensus conference, which regards sepsis as a systemic response to infection. The term systemic inflammatory response syndrome (SIRS) was also introduced to describe the inflammatory process.[6] SIRS includes:

1. A body temperature greater than 38oC or less than 36oC.
2. A heart rate greater than 90 beats per minute.
3. Tachypnea is manifested by a respiratory rate greater than 20 breaths per minute or hyperventilation, as indicated by a PaCO2 of less than 32 mmHg.
4. A white blood cell counts greater than 12 000/mm^2 or less than 4 000/mm^2 or the presence of more than 10% immature neutrophils.

According to the consensus in 1992, a diagnosis of sepsis is made when SIRS (≥ 2 criteria met) is the result of a confirmed infection. This diagnosis criterion helped to provide clinicians with a bedside tool for early recognition and treatment as well as to serve as a clear criterion for research purposes. Several drawbacks unfold as this diagnosis is applied into clinical practice. SIRS criteria happen commonly in hospitalized patients, with or without infection. A large study the United States examined SIRS in ward patients and the result showed a forty seven percent of them satisfied at least two of SIRS criteria during their stay.[7] This result showed that SIRS criteria are poorly specific for sepsis. Even though a large number of hospitalized patients met SIRS criteria, one over eight severe sepsis patients that were SIRS-negative and carried grim prognosis.[8]

In addition to the non-specific as well as non-sensitive nature of sepsis criteria developed in 1992, our understanding of the pathophysiology of sepsis had increased substantially since. It was thought to be a result of a hyperinflammatory state of the body to infection. This notion started as a study demonstrated the induction of shock and tissue injury with recombinant human cachectin (TNFα) to animals.[9] During the 1990s, TNFα became a promising therapeutic target for treatment of sepsis but the results from its' studies were disappointing. A study, published on New England Journal of Medicine, using fusion protein as

TNF receptor showed no difference in survival between control and intervention group.[10] INTERSEPT, a large international randomized controlled trial in 1996, tested the efficacy of monoclonal antibody against TNFα in the treatment of sepsis. No significant improvement was observed for the intervention group.[11]

With the failure to observe any benefits in suppressing the immune system during sepsis, researchers started to explore the possibility of an immunosuppressive state in patients with sepsis. Sepsis-induced immunosuppression and how it can affect the body response to infection were first addressed in a comprehensive review by Hotchkiss R. S. in 2003.[12] He stated in his review that sepsis-induced apoptosis of immune cells was found in multiple organs of patients dying of sepsis and this process was also later confirmed with post-mortem studies. The massive depletion of immune cells including CD4+, CD8+ T cells, and dendritic cells leads to immunosuppression in these patients. In addition, the triggers for apoptosis in sepsis do not come from a single pathway. Both death receptor mediated pathway and mitochondrial-mediated pathway were found to be able to activate apoptotic process.[13] These findings can explain why the effort to suppress the immune system in the 1990s did not produce any observable benefit.

The 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference stated clearly that they realized using SIRS criteria for sepsis is overly sensitive and nonspecific and the definition for sepsis may need to be refined to better illustrate the extensive clinical manifestations of sepsis in practice.[14] However, no new definition for sepsis was proposed in this conference.

The third international consensus including four meetings between experts in sepsis was organized between January 2014 to January 2015. The conclusion of this conference reflected outstanding advances in the field of sepsis since the 2001 conference. One of the major updates is the new definition of sepsis as well as the new diagnosis criteria for sepsis. According to this conference, Sequential Organ Failure Assessment or Sepsis-related Organ Failure Assessment (SOFA) score can be used as an assessment tool for organ dysfunction in patients with confirmed infection and if SOFA score increases two points or more above baseline, patients can be diagnosed with sepsis.[5]

Sepsis-related Organ Failure Assessment (SOFA) was a direct result from a consensus meeting in 1994 of the ESICM. They decided to create a scoring system to quantify the severity of organ failure in sepsis and chose six organs including respiration, coagulation, liver, cardiovascular, central nervous system, and renal system. The relationship between SOFA score

and mortality was recorded from 1643 patients admitted to the ICU for sepsis. This research showed an increase in mortality rate as SOFA score becomes higher.[15] Moreover, a prospective observational study in Belgium later confirmed the relationship of SOFA score and mortality rate in critically ill patients with or without sepsis. From this result, they recommended that SOFA score can be a good predictor of outcome due to its strong relationship with mortality. They believed that this scoring system meets several characteristics of a useful prognosis tool including:

- Each organ's function varies depending on the severity of illness. It is not an all-or-nothing phenomenon.
- Any tool used to quantitatively measure each organ's function needs to be easily accessible and repeatable.
- Organ's dysfunction also varies with time and progression of patient's illness.[16]

After showing it's robustness in prediction of mortality, SOFA score had been extensively studied and a systematic review of eighteen studies published in 2009 show an AUC ranging from 0.61 to 0.88 for SOFA-based models.[17] For patients with sepsis, the AUC for SOFA was found to be 0.868.[18]

SOFA score includes 6 organs with points ranging from 0 to 4. Zero-point means normal function while 4 points mean severe dysfunction. These organs and their respective value are respiratory system (PaO2/FiO2), cardiovascular system (MAP and the use of vasopressors), hepatic system (bilirubin), coagulation system (platelet count), renal system (creatinine or urine output), and neurological system (Glassgow Coma Scale).

Sepsis severity can range from mild derangement of an organ system to severe derangement of multiple organ systems. In 1992, two terms were introduced to describe the continuum of sepsis severity including severe sepsis and septic shock. Severe sepsis is defined as sepsis with organ dysfunction, sepsis-induced hypotension, or hypoperfusion abnormalities including lactic acidosis, oliguria, and acute alteration of mental status. Septic shock is diagnosed when the patients still require inotropes or vasopressors after adequate fluid resuscitation.[6] However, with the new definition of sepsis in 2016, the task force concluded that the term "severe sepsis" is superfluous. Only the term "septic shock" remained with similar definition and it is used to describe a condition in which the patients have much worse outcome.[5]

1.1.2 Epidemiology and prognosis of sepsis

A review of national discharge records in the United States from 1979 to 2000 reported the incidence of sepsis was 82.7 per 100,000 population in 1979, which increased to 240.4 per 100,000 population in 2000. However, the mortality rate decreased from 27.8 percent during 1979 – 1984 to 17.9 percent during 1995 – 2000. In this review, male sex is a risk factor for sepsis with a relative risk of 1.28.[19]

In 2020, a study on global burden of disease was published and, in their paper, sepsis was accounted for 19.7% of global death. The incidence reported in this study was 1074.7 cases per 100,000 in 1990 and was reduced to 677.5 cases per 100,000 in 2017. Sepsis is more prevalent during early childhood and older age. However, this study found a higher incidence of sepsis in female. The most common cause of sepsis was found to be diarrheal disease, but the most common underlying cause of sepsis-related death was respiratory infection.[20]

In addition to its high incidence, sepsis' mortality rate is also quite high. A systematic review for articles between 2009 and 2019 in Europe, North America, and Australia reported that a 30-day mortality rate of sepsis and septic shock are 24.4% and 34.7%, respectively. The 90-day mortality of sepsis and septic shock of this cohort was also recorded at 32.2% and 38.5%, respectively.[21] Nevertheless, the reported mortality rate of sepsis and septic shock have been known to vary significantly from studies to studies. For example, a mortality rate of up to fifty percent was recorded in a study of Dr. Kadri using hospital records from 27 academic hospitals in the United States.[22]

In Vietnam, there has been few research on the incidence of sepsis and septic shock. From the global report in 2020, South Asia and East Asia were among the regions with highest burden of sepsis.[20] A study from Can Tho Central General Hospital with a cohort of 150 patients admitted to the ICU from May 2016 to May 2018 reported a high mortality rate of 62% for septic shock.[23] Another study testing prognostic accuracy of multiple scoring systems in mortality prediction of sepsis found an overall mortality rate of 37.6%. Within this cohort, 72.6% of patients were diagnosed with septic shock and 27.4% of patients were diagnosed with sepsis.[24]

It was found that patients with obesity not only carry significantly higher risk of infection of multiple sources, but also have worse prognosis compared to normal weight patients.[25] The incidence of sepsis was also found to be increased disproportionately in older age patients. In addition, age is an independent predictor of mortality.[26]

In general, sepsis is a major health concern in both developed and developing countries with high incidence rate and high mortality rates. With advances in diagnosing and treating sepsis, we now know that its' burden to society is beyond the acute phase. Its' sequalae decrease patients' quality of life as well as increase cardiovascular risk of affected patients.[27] This led to a tremendous economic burden for the patients, their family as well as society.

1.1.3 Prognostic tool for mortality prediction in sepsis

Due to its high incidence as well as high mortality rate, sepsis has been a major healthcare issue for a long time. Even for patients who survive sepsis, several research show a subsequently bad long-term outcomes including death and disability. For example, a large nationwide population-based study in Taiwan showed a hazard ratio of 2.18 for all-cause mortality one year after discharge. This holds true even when compared with non-sepsis hospitalized patients and this trend persisted for up to 5 years.[28] When comparing cardiovascular outcomes, sepsis survivors carry 1.77 higher risk of myocardial infarction, 1.67 higher risk of stroke, and 1.65 higher risk of heart failure according to systematic review by Dr. Kosyakovsky L. B.[27]

It is important to have an easily accessible tool to prognosticate sepsis for several reasons. First, due to sepsis' high burden, a good prognostic tool can help allocating resources to treat sepsis patients. Second, it can help identify high-risk patients to guide a more intensive treatment to better the outcome of these patients. Finally, with better resources allocation and treatment, we can hopefully reduce post-sepsis complications.

SOFA has been the most extensively used and proven scoring system for sepsis. Due to its' high AUC in predicting mortality, SOFA has also been used to compare with other scoring systems and other promising biomarkers. Other scoring systems that have been validated in multiple studies are APACHE II, SAPS II, and mNUTRIC score. APACHE II was created in 1985 as a severity classification tool for patients admitted to intensive care unit.[29] The AUC of APACHE II was reported to be 0.80 in a retrospective study of 2054 patients from a medical intensive care unit in the United States.[30] Moreover, when compared to SOFA score, APACHE II showed equivalent power in predicting mortality in sepsis patients.[31] Similar predictive value was found for SAPS II and mNUTRIC with variable range of AUC. These scoring systems were applied to Vietnamese population in the research of Dr. Pham D. Hai and the AUC for SOFA, APACHE II, SAPS II, and mNUTRIC are 0.77, 0.78, 0.73, and 0.79, respectively.[24] Considering similar predictive values of these scoring systems, SOFA is the best scoring system for sepsis due to its' ease of calculation and repeatability.

1.2 NEUTROPHIL TO LYMPHOCYTE RATIO IN SEPSIS

1.2.1 Physiological response of neutrophils

Neutrophils belong to the granulocyte group of white blood cells. They origin from bone marrow and represent 45-74% of leukocyte counts. Without any insult, most neutrophils are stored in the bone marrow (~90%) and only 2-3% are within the circulation. Inside the circulation, about half of the neutrophils flow freely while the other half marginate on the endothelium. They circulate for a short amount of time (6 – 7 hours) and become senescent. They are then cleared by macrophages in the lung and the spleen. Certain signals that can mobilize neutrophils from the bone marrow are IL-1, TNF-α, the CSFs, complement fragments, and chemokines.[32]

In response to infection, the number of circulating neutrophils increases and several stimuli from endothelial cells, other leukocytes, or bacterial products can promote the adhesiveness of these neutrophils and localize them to the infection site. Once at the infection site, they can directly attack the pathogen through several mechanisms including phagocytosis, degranulation, release of antimicrobial proteins, … The term to describe the condition in which the absolute number of neutrophil increases in the circulation is neutrophilia.

On the other hand, the decreased absolute number of neutrophils in circulation (termed neutropenia) can happen in many situations. First, it is well known that certain viral infections can decrease neutrophil counts. These includes influenza type A, influenza type B, dengue fever, measles, rotavirus, and EBV.[33] Some bacterial infections can also manifest with neutropenia. For example, infection with tuberculosis, tularemia, or rickettsial pox can have neutropenia. Second, many medications, especially anti-cancer medications, can cause neutropenia. Third, congenital diseases, rheumatologic disorders, or hematologic malignancies can also cause neutropenia.[34]

1.2.2 Physiological response of lymphocytes

Lymphocytes are another subgroup of white blood cells. They are divided into three subgroups including T lymphocytes, B lymphocytes, and natural killer (NK) cells. T cells originated from the thymus while B cells and NK cells originate from the bone marrow. T cells and B cells play a major role in the adaptive immune system. NK cells, however, are part of innate immunity. Even though they all have similar morphology, they differ significantly in their surface antigen as well as intracellular protein expression. This results in their different function.[32]

Natural killer cells kill target cells by releasing cytotoxic granules as they recognized through several surface molecules. The lack of major histocompatibility class I molecules also mark certain tumor cells as natural killer cells' target. They can also produce many cytokines (IL-3, IL-5, IL-8…), IFN-γ, M-CSF, and chemokines. NK cells not only react to infectious agents early in the course, but they also partly regulate the response of T cells, B cells, and the adaptive immune system.[32]

A paper studying leukocyte changes in septic shock using flow cytometry found a significant leukocytosis during the first 48 hours. This major change is due to the elevated number of circulating neutrophils. In contrast, a marked decrease in absolute lymphocyte counts was observed at inclusion and remained at a very low during monitoring time. This decrease can be observed in all lineages of lymphocyte including T cells, B cells, and NK cells. Within T lymphocytes, CD4+ and CD8+ T-cell both decreased in a similar fashion. Monocyte counts did not change and are comparable to normal values.[4] An observational study also demonstrated a drastic reduction of T CD4+ lineages (CD25+ and CD25-) in septic shock patients and an increased percentage of Treg which they hypothesized due to Treg's resistance to apoptosis.[35] Using real time RT-PCR to monitor the expression of two transcription factors including T-bet and GATA3 in peripheral blood, Dr. Pachot et al found significantly diminishing levels of them in septic shock patients. The authors suggested this result can confirm a state of sepsis-induced immune paralysis with greatly reduced number of Th1 and Th2 cells.[36]

1.2.3 Neutrophil to lymphocyte ratio

During sepsis or septic shock, many complicated processes happen and many of them, separately or together, can affect the mortality of patients. The two major states that current research is studying are the hyperinflammatory state and the immune-paralysis state. Hyperinflammatory state is demonstrated by massive release of cytokines and chemokines that in turn damages multiple organs further away from the infection site. On the other hand, immune paralysis is characterized by the drastic reduction in several immune cell lineages, especially T lymphocytes, which may lead to the defect of the patients' adaptive immunity to fight against infection. There is currently no quantitative method to measure the severity of hyperinflammatory or immune paralysis of sepsis patients.

From observation from multiple studies about neutrophilia and lymphocytopenia in critically ill patients, especially sepsis patients, Zahorec R. introduced the concept of neutrophil to lymphocyte ratio (NLR) as a simple index to evaluate severity of SIRS as well as sepsis.[37] NLR is calculated by dividing the absolute count of neutrophils by the absolute count of

lymphocytes which are collected from peripheral complete blood count. Multiple studies were carried out to find normal values for NLR in different populations. One of the largest studies to find normal values for NLR was conducted in New York state of America. The researchers found that the mean NLR of 9,427 citizens of New York state is 2.15. The average neutrophil counts and lymphocyte counts are 4,300/µl and 2,100/µl, respectively. Beside differences in races, this study also found a significantly higher NLR in diabetes, cardiovascular disease, and smoking.[38] For Asian population, data from 12,160 healthy South Korean adults routine blood analysis was collected and showed a mean NLR of 1.65. There was no significant differences between age groups and sex.[39] The result from South Korean population in slightly lower compared to the New York state population. This is consistent with subgroup analysis of the New York state as Whites have higher mean NLR compared to other races.

1.3 NEUTROPHIL TO LYMPHOCYTE RATIO IN CLINICAL PRACTICE

1.3.1 Current applications of neutrophil to lymphocyte ratio

The latest update on sepsis guideline in 2021 mentioned the need for palliative care consultation based on clinician's judgement as well as the need for family member support.[40] Multiple scoring systems have been validated and applied into clinical practice to better prognosticate sepsis patients. Those includes SOFA, APACHE II, SAPS II, mNUTRIC, … In addition, during the third international consensus meeting, quick SOFA (qSOFA) was introduced as a tool to diagnose sepsis at bedside in ward patients. qSOFA includes:[5]

- Glassgow coma score of 13 or less.
- Systolic blood pressure of 100mmHg or less.
- Respiratory rate of 22 or more.

The patient is considered positive for qSOFA if they meet two or more of these criteria. Experts from the consensus believed that with qSOFA can become a simplified version of SOFA score and may add good predictive value for sepsis diagnosis outside of the ICU.[5] However, later research found a consistent result of low sensitivity for sepsis diagnosis and prognosis. For example, a recent meta-analysis of 57 studies showed that qSOFA has a sensitivity of 42% for sepsis diagnosis and 41% for sepsis mortality. This can essentially exclude qSOFA as a screening tool outside of the ICU as originally introduced. However, good specificity for sepsis mortality (88%) preserves qSOFA as an acceptable tool for prognostic purposes.[41]

There are several problems with using scoring systems to prognosticate sepsis and septic shock. First, APACHE II requires 12 indices including multiple clinical data and laboratory tests. SOFA is quite simpler; however, it still requires arterial blood gas which may not be

available in resource-limited areas. Obtaining these scoring systems takes time. Moreover, if we want to use these scoring systems as follow-up to disease progression after treatment, we will need extensive testing which is costly and not feasible in resource-limited area. Second, even though these systems have been proven that higher score correlates to sepsis mortality and can be used to predict mortality in sepsis, their sensitivity and specificity vary among researches. The heterogeneity of sepsis and septic shock can partly explain this. Finally, due partly to sepsis' complexity and dynamic nature, there is no gold standard for diagnosis and no proven single tool that can be used to prognosticate sepsis mortality. That is why current research is continuously working on finding new biomarkers or scoring systems for sepsis prognosis.

The value of NLR in critically ill patients was demonstrated in a study published in 2014. Akilli et al. created a prospective, observational study on 373 emergency patients and found a hazard ratio of 1.63 for in-hospital mortality and 1.58 for 6-month mortality for patients with NLR of 11.9 or higher. With the receiver operating characteristics curve, an NLR cut-off of 11.9 was obtained, and the area under the curve was 0.61. Within this cohort, patients with an NLR lower than 11.9 were less likely to develop sepsis (19.5%) compared to patients with an NLR of 11.9 or higher (29.6%).[42]

A meta-analysis published in 2020, including 14 studies and 11,564 patients, showed an association between high NLR and poor prognosis in sepsis patients. They found a hazard ratio of 1.75 (95% CI, 1.56 – 1.97, $p<0.01$) between non-survivors and survivors with no significant heterogeneity. Different NLR cutoffs ranging from 4.36 to 23.8 were used in the studies. As a result, no ideal cut-off can be concluded from this research.[3] This showed the robustness of the prognostic value of NLR in sepsis patients, as its' validity holds in different populations. However, there is a variation among normal values of NLR among different races, which may affect the cutoff of NLR in critical conditions like sepsis. Besides, different cut-offs provide different levels of sensitivity and specificity for sepsis mortality prediction.

As stated before, the simplicity of calculating NLR and its' repeatability make NLR an excellent prognostic tool to be used in combination with other scoring systems and biomarkers in resource-limited areas. Now, there is no published research validating NLR in the Vietnamese population. It is important to validate the prognostic value of NLR in the Vietnamese population as well as to find a cut-off with good sensitivity and specificity for sepsis mortality.

1.3.2 Current research in neutrophil to lymphocyte ratio and sepsis

In 2001, Zahorec R. first described the dynamic relation between NLR and systemic inflammation and stress in critically ill patients.[37] Multiple studies explored the application of NLR in diagnosing bacteremia, infection, and sepsis. Gurol et al. reported an NLR's AUC of 0.751 in diagnosing sepsis and found a correlation between NLR and procalcitonin, CRP, and WBC.[43] Salciccioli et al. described an association between NLR and mortality in critically ill patients. When split into quartiles, the ORs for 28-day mortality of quantiles two, three, and four compared to one were 1.30, 1.75, and 2.70, respectively.[44] Jager et al. used ROC curve analysis for predicting mortality and reported an AUC of 0.701 for NLR in patients with community-acquired pneumonia.[45]

In 2020, Huang et al. published a meta-analysis that included 14 studies and 11 564 patients to evaluate the prognostic value of NLR in sepsis. The study showed that higher NLR was associated with poor prognosis in patients with sepsis with a hazard ratio of 1.75 and a 95% CI of 1.56-1.97.[3] Lorente et al. used multiple logistic regression analyses and found that NLR on day 1, day 4, and day 8 were independent predictors of mortality.[46] Similar results were reported in a study in Egypt with multivariate logistic regression analysis of NLR and possible cofounders. The authors found an NLR's AUC of 0.695 for predicting poor outcomes and confirmed that NLR was an independent mortality predictor.[47] Many recent studies also used logistic regression to evaluate the prognostic value of NLR in predicting mortality in patients with sepsis. The results consistently showed reasonable prognostic value of NLR with varied AUCs and cut-offs.[48–50]

To the best of our knowledge, there is no study in Vietnam describing the changes in NLR in patients with sepsis or validating the prognostic value of NLR in predicting sepsis mortality.

CHAPTER 2. METHODOLOGY

2.1 METHOD

2.1.1 Study design

This is a single-center, retrospective, observational study conducted at the Medical Intensive Care Unit at 108 Central Military Hospital.

2.1.2 Study population

The study population includes all patients admitted to the Medical Intensive Care Unit at 108 Central Military Hospital, Hanoi, Vietnam, with a diagnosis of sepsis or septic shock from January 2021 to December 2022.

Data from the patients were collected chronologically without regard to age, sex, or outcome.

2.1.3 Inclusion criteria

All patients above the age of 18 admitted to the Medical Intensive Care Unit of 108 Central Military Hospital met the diagnostic criteria of Sepsis-3 published by the American Society for Critical Care Medicine and the European Society for Critical Care Medicine in 2016 and had been diagnosed with sepsis or septic shock.

2.1.4 Exclusion criteria

- Patients who were on corticosteroids within seven days of diagnosis.
- Patients who had cardiac arrest before admission.
- Patients who were diagnosed with sepsis or septic shock over 24 hours.
- Patients who died within 24 hours of presentation without a definite diagnosis.
- Patients who had been diagnosed with autoimmune diseases.
- Patients who had active cancer or received cancer treatment within 5 years of diagnosis.
- Patients who had been diagnosed with hematological disorders.

2.1.5 Sample size

This is a descriptive study, so we will collect as many patients who meet the inclusion criteria as possible.

2.1.6 Study equipment

- Preprinted SOFA, APACHE II, and SAPS II scores for easy access.
- Preprinted criteria for sepsis, septic shock and AKI.
- Preprinted data collection forms.

2.2 STUDY CONTENT

2.2.1 Evaluation criteria

❖ **General characteristics of the study population:**

♦ **Evaluation criteria:**

- Demographic data, clinical data of the study population

+ Information regarding age, sex, infection source, hemodynamics, severity scores (SOFA, APACHE II, SAPS II scores).

+ Characteristics of complete blood count, liver function test, renal function test, glucose, lactate, procalcitonin, microbiological result.

- Clinical information, lab values related to mortality in sepsis and septic shock patients.
- Treatment outcomes including hospitalization days, mechanical ventilation rate, mechanical ventilation days, CRRT rate, and mortality.
- Death criteria: irreversible cessation of circulatory and respiratory function in hospital.
- All patients were treated according to the standard treatment procotol of Medical Intensive Care Unit of 108 Central Military Hospital.

❖ **Objective 1: changes in NLR in patients with sepsis or septic shock**

Content: *changes in NLR in patients with sepsis or septic shock*

♦ **Evaluation criteria:**

- NLR at different time point: at time of sepsis or septic shock diagnosis (T0) and between 48-72 hours (T1).
- NLR according to age groups (≤ 65 years old and > 65 years old).
- NLR according to sex (male and female).
- NLR according to organ dysfunction (kidney and liver).
- NLR according to blood culture result (positive or negative).
- NLR of survivors and non-survivors.

❖ **Objective 2: Correlation of NLR with other predictive values for severity and in-hospital mortality in patients with sepsis and septic shock.**

Content 1: *Correlation of NLR and other predictive values for severity and mortality in patients with sepsis and septic shock.*

♦ **Evaluation criteria:**

- Correlation of NLR at T0 with severity scoring systems (SOFA, APACHE II, SAPS II) at T0 in patients with sepsis and septic shock.
- Correlation of NLR at T0 and biological markers for severity (bilirubin, lactate) at T0 in patients with sepsis and septic shock.

Content 2: *NLR prognostic value for in-hospital mortality in patients with sepsis and septic shock.*

♦ **Evaluation criteria**

- Find sensitivity, specificity, cut-off, and area under the curve in ROC analysis of NLR in in-hospital mortality prediction at T0 and compare with other severity scoring systems.
- Find sensitivity, specificity, cut-off, and area under the curve in ROC analysis of NLR in in-hospital mortality prediction at T0 and compare with biological markers for disease severity (bilirubin, albumin, and lactate) at T0.
- Find ROC curve for in-hospital mortality when NLR is combined with other severity scoring systems and compare with NLR alone.
- Find AUCs of each variable for comparison.
- Use univariate logistic regression and multivariate logistic regression to find independent predictors of in-hospital mortality of patients with sepsis and septic shock.

2.2.2 Data collection

❖ **Timing of clinical data collection:**

- Time T0: at the time of diagnosis of sepsis or septic shock.
- Time T1: on day 3 of hospitalization (between 48-72 hours from admission).

❖ **Patients collection into the study:**

All patients admitted to 108 Central Military Hospital had an electronic record. The researcher will use electronic medical records to sort all patients admitted to the Medical Intensive Care Unit of 108 Central Military Hospital with the diagnosis of sepsis or septic shock on admission. The researcher will then check if the patients met Sepsis-3 criteria and had no exclusion criteria.

❖ **Prepare research form for each patient:**

After the patient fulfills the requirement and is included in the research, a research form will be prepared with the following information:

- Name, age, sex, admission date, address, hospital identification number.
- Diagnosis, weight, height, source of infection, comorbidities, in-hospital mortality outcome, and hospitalization days.
- Vitals signs, vasopressor/inotropes dose, Glasgow Coma Score, mechanical ventilator, vasopressor days, and mechanical ventilation days.
- Complete blood counts and differentials include WBC, neutrophil count, lymphocyte count, RBC, Hgb, Hct, RDW, PLT, and MPV. If there are multiple CBCs within the collection time frame, highest NLR was chosen for the research.

- Panel biochemistries include glucose, urea, creatinine, AST, ALT, total bilirubin, albumin, ions panel, and procalcitonin.
- Result of arterial blood gas and blood culture.

2.2.3 Definition of variables, criteria used in research

❖ Sepsis and septic shock diagnosis:[5]

	SEPSIS	SEPTIC SHOCK
2015 Clinical criteria	Suspected or documented infection and an acute increase ≥ 2 SOFA points	Sepsis and vasopressor therapy needed to elevate MAP ≥65 mmHg and lactate >2 mmol/L (18mg/dL) despite adequate fluid resuscitation

❖ **Acute Kidney Injury Network criteria for acute kidney injury:**

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of ≥0.3 mg/dl or increase to ≥150 to 200% from baseline	Urine output <0.5 ml/kg/h × 6 h
2	Increase in serum creatinine to >200 to 300% from baseline	Urine output <0.5 ml/kg/h × 12 h
3	Increase in serum creatinine to >300% from baseline (or serum creatinine of ≥4.0 mg/dl with an acute increase of at least 0.5 mg/dl)	Urine output <0.3 ml/kg/h × 24 h or anuria × 12 h

Figure 2.1 Criteria for AKI

❖ **Sequential organ failure assessment (SOFA):**[5]

System	Score 0	1	2	3	4
Respiration					
PaO_2/FIO_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL/d				<500	<200

Figure 2.2 Variables in SOFA

❖ **Acute physiology and chronic health evaluation II (APACHE II):**[29]

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE +4	+3	+2	+1	0	LOW ABNORMAL RANGE +1	+2	+3	+4
TEMPERATURE — rectal (°C)	≥41°	39°-40.9°		38.5°-38.9°	36°-38.4°	34°-35.9°	32°-33.9°	30°-31.9°	≤29.9°
MEAN ARTERIAL PRESSURE — mm Hg	≥160	130-159	110-129		70-109		50-69		≤49
HEART RATE (ventricular response)	≥180	140-179	110-139		70-109		55-69	40-54	≤39
RESPIRATORY RATE — (non-ventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
OXYGENATION: A-aDO_2 or PaO_2 (mm Hg) a. $FiO_2 \geq 0.5$ record A-aDO_2	≥500	350-499	200-349		<200				
b. $FiO_2 < 0.5$ record only PaO_2					PO_2 > 70	PO_2 61-70		PO_2 55-60	PO_2 < 55
ARTERIAL pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
SERUM SODIUM (mMol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
SERUM POTASSIUM (mMol/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5
SERUM CREATININE (mg/100 ml) (Double point score for **acute** renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		< 0.6		
HEMATOCRIT (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		< 20
WHITE BLOOD COUNT (total/mm3) (in 1,000s)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
GLASGOW COMA SCORE (GCS): Score = 15 minus actual GCS									
[A] Total ACUTE PHYSIOLOGY SCORE (APS): Sum of the 12 individual variable points									
Serum HCO_3 (venous-mMol/L) [Not preferred, use if no ABGs]	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	< 15

[B] **AGE POINTS:** Assign points to age as follows:

AGE(yrs)	Points
≤44	0
45-54	2
55-64	3
65-74	5
≥75	6

[C] **CHRONIC HEALTH POINTS**
If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows:
a. for nonoperative or emergency postoperative patients — 5 points
or
b. for elective postoperative patients — 2 points

DEFINITIONS
Organ insufficiency or immuno-compromised state must have been evident **prior** to this hospital admission and conform to the following criteria:

LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.

CARDIOVASCULAR: New York Heart Association Class IV.

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg), or respirator dependency.

RENAL: Receiving chronic dialysis.

IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection, e.g., immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS.

APACHE II SCORE
Sum of [A] + [B] + [C]
[A] APS points
[B] Age points
[C] Chronic Health points
Total APACHE II

Figure 2.3 Variables in APACHE II

❖ **Simplified acute physiology score (SAPS II):**[51]

Variable				Value (score)
Heart Rate (/m)			<40 (11)	40-69 (2)
Systolic BP (mmHg)			<70 (13)	70-99 (5)
Temperature				
PO_2/Fio_2 (%)	<100 (11)	100-199 (9)	>200 (6)	
Urine Output		<500 (11)	>500 (4)	
BUN				
WBC ($x10^3/mm^3$)				<1 (12)
Potassium (mmol/L)				<3 (3)
Sodium (mmol/L)				<125 (5)
HCO^3 (mmol/L)			<15 (6)	15-19 (3)
Bilirubin				
GCS	<6 (26)	6-8 (13)	9-10 (7)	11-13 (5)

Age (score)
<40 (0)
40-59 (7)
60-69 (12)
70-74 (15)
75-79 (16)
>80 (18)

Chronic disease:
Metastatic cancer-9
Hemat.malig-10
AIDS-17

Figure 2.4 Variables in SAPS II

❖ **Modified nutrition risk in critically ill (mNUTRIC):**[52]

Variable	Range	Points
Age (years)	Below 50	0
	From 50 to 74	1
	75 and more	2
APACHE II (points)	Below 15	0
	From 15 to 19	1
	From 20 to 27	2
	28 and more	3
SOFA (points)	Below 6	0
	From 6 to 9	1
	10 and more	2
Co-morbidities (n)	0, 1	0
	2 and more	1
Days before ICU admission	0	0
	1 and more	1

Figure 2.5 Variables in mNUTRIC

2.2.4 Statistical analysis

We used EpiData 3.1 for data input. We used Epi Info version 7.6.0.2, IBM SPSS Statistics 26, and Medcalc version 18.2.1 for data analysis.

SOFA score, APACHE II score, SAPS II score, and mNUTRIC score were calculated within 24 hours of ICU admission.

Categorical variables were described as frequencies (percentages). Continuous variables were introduced as mean values ± standard deviation (SD) for parametric variables or median (interquartile range) for nonparametric variables. Categorical variables were analyzed with the chi-square test or the Fisher's exact test as appropriate. Normally distributed data was analyzed with the student's *t*-test, and non-normally distributed data was analyzed with the Mann-Whitney test.

Receiver operating characteristics (ROC) curve was used to calculate area under the curve of NLR and other variables for predicting in-hospital mortality. DeLong's test was used to compare areas under the curve of different variables. The best cut-off value was chosen as the maximum value of the sum of sensitivity and specificity.

Univariate and multivariate logistic regression was used to identify independent predictors of in-hospital mortality.

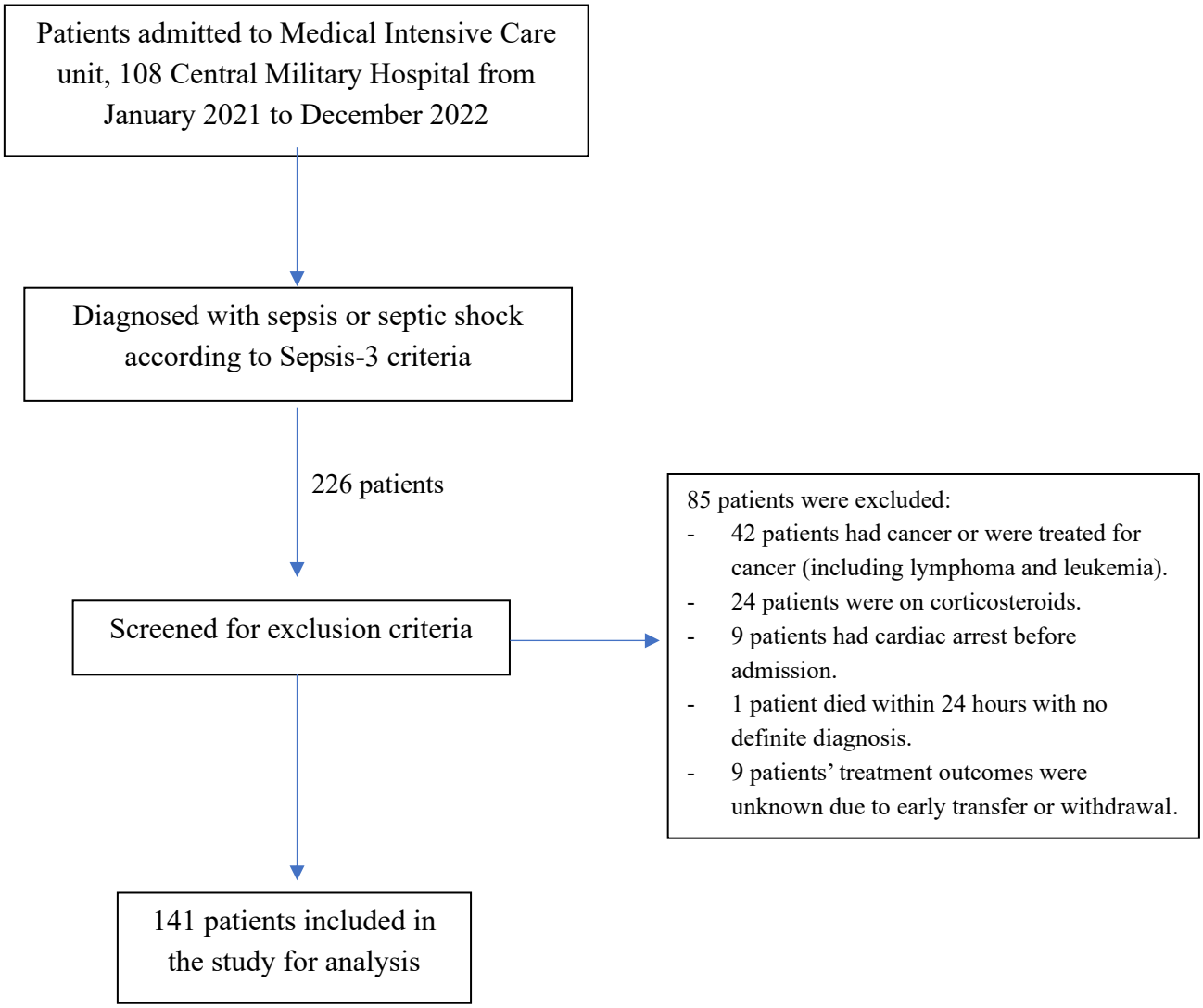
The result was considered significant when p-value is less than 0.05.

2.2.5 Study ethics

This study collects data demographic data and lab tests data retrospectively. Collected data is securely kept by the researcher and remains confidential. The process of collecting data, analyzing data as well as the results of the research does not affect the patient's treatment in any way.

The research proposal was approved by the institutional review board of VinUniversity and the ethics committee of 108 Central Military Hospital (6747/QĐ-BV). Due to the nature of this retrospective observational study, the consent form is waived.

2.2.6 Research diagram



CHAPTER 3. STUDY RESULTS

3.1 GENERAL CHARACTERISTICS

Table 3.1 Characteristics of sex, age, and number of comorbidities in the study group

		All		Sepsis (n = 28)		Septic shock (n= 113)		p-value
		n	%	n	%	n	%	
Sex	Male	99	70.2	20	71.4	79	69.9	p > 0.05
	Female	42	29.8	8	28.6	34	30.1	
Mean Age (year) (X ± SD) (min-max)		72.0 ± 14.1 (20 – 99)		75.3 ± 12.3 (49-99)		71.2 ± 14.5 (20 – 99)		p > 0.05
Number of comorbidities (X ± SD)		1.62 ± 1.25		1.93 ± 1.18		1.55 ± 1.26		p > 0.05

Comment:

Males comprised most of our study population. The overall percentage of males was 70.2%, 2.3 times higher than females. Within the sepsis and septic shock groups, a similar distribution was observed. There was no significant difference in sex between sepsis and septic shock groups ($p > 0.05$).

The mean age was 75.3 for the sepsis group and 71.2 for the septic shock group. There was no significant difference in age between the two groups ($p > 0.05$). The youngest patient was 20-year-old while the oldest patient was 99-year-old.

The mean number of comorbidities was 1.62 and did not differ significantly between sepsis and septic shock patients.

There were 31 patients (21.99%) with no comorbidity. The other patients had several comorbidities ranging from 1 disease up to 5 diseases.

Table 3.2 Prevalence of comorbidities in the study group

Past medical history	All		Sepsis (n = 28)		Septic shock (n= 113)		p-value
	n	%	n	%	n	%	
Hypertension	75	*53.2*	19	*67.9*	56	*49.6*	p > 0.05
Diabetes	50	*35.5*	9	*32.1*	41	*36.3*	p > 0.05
Stroke	28	*19.9*	7	*25.0*	21	*18.6*	p > 0.05
Coronary artery disease	8	*5.7*	1	*3.6*	7	*6.2*	p > 0.05
Heart failure	12	*8.5*	3	*10.7*	9	*8.0*	p > 0.05
COPD	6	*4.3*	2	*7.1*	4	*3.5*	p > 0.05
Cirrhosis	3	*2.1*	0	*0.0*	3	*2.7*	p > 0.05
CKD	19	*13.5*	4	*14.3*	15	*13.3*	p > 0.05

Comment:

The most common comorbidity was hypertension, with 53.2% of our cohort. Diabetes, stroke, and chronic kidney were also quite common at 35.5%, 19.9%, and 13.5%, respectively.

Between the sepsis and septic shock group, there was no significant difference in in the rate of hypertension, diabetes, stroke, coronary artery disease, hearth failure, COPD, cirrhosis, and chronic kidney disease (p > 0.05).

Table 3.3 Distribution of infection sources in the study group

Source of infection	All		Sepsis (n = 28)		Septic shock (n= 113)		p value
	n	%	n	%	n	%	
Pulmonary	63	*44.7*	14	*50.0*	49	*43.4*	p > 0.05
Gastrointestinal	28	*19.9*	4	*14.3*	24	*21.2*	
Urinary	26	*18.4*	7	*25.0*	19	*16.8*	

Skin and soft tissue	7	*5.0*	1	*3.6*	6	*5.3*	p > 0.05
Others	17	*12.1*	2	*7.1*	15	*13.3*	

Comment:

Pulmonary source was the most common infection site which accounts for 44.7% of the cohort. The second most common infection source in sepsis group was urinary source while the second most common infection source in septic shock group was gastrointestinal source. However, there was no significant difference in distribution of infection sources between two groups (p > 0.05).

Table 3.4 Hemodynamic characteristics in the study group

Parameter	**All**	**Sepsis (n = 28)**	**Septic shock (n= 113)**	**p-value**
	Median *(Interquartile range)*	**Median *(Interquartile range)***	**Median* *(Interquartile range)***	
Hearth rate (bpm)	110 (95 – 129)	100 (90 – 115)	110 (99 – 130)	p > 0.05
Systolic BP (mmHg)	107 (94 – 120)	115 (96 – 140)	105 (90 – 120)	**p = 0.01**
Diastolic BP (mmHg)	60 (50 – 70)	69 (60 – 80)	60 (50 – 70)	**p < 0.01**
Mean BP (mmHg)	77 (70 – 86)	86 (70 – 98)	73 (70 – 83)	**p < 0.01**

*All patients were either on vasopressors or inotropes.

Comment:

All patients in septic shock required the support of vasopressor or inotrope. Three septic shock patients (2.1%) required more than one vasopressor/inotrope. The most common vasopressor was norepinephrine.

Even though all septic shock patients were either on vasopressor, inotropes, or both, their median systolic blood pressure, median diastolic pressure, and median, mean blood pressure were significantly lower than sepsis patients (p < 0.05).

The heart rate of septic shock patients was slightly higher than that of sepsis patients but was not significant (p > 0.05).

Table 3.5 Characteristics of complete blood count and differentials in the study group

Parameter	All	Sepsis (n = 28)	Septic shock (n = 113)	p-value
	Median ***(Interquartile range)***	**Median** ***(Interquartile range)***	**Median** ***(Interquartile range)***	
WBC (G/L)	14.74 (9.07 – 20.85)	13.65 (8.34 – 21.47)	15.20 (9.69 – 20.84)	p > 0.05
NEU (G/L)	13.39 (8.02 – 18.85)	11.68 (7.00 – 19.03)	13.93 (8.57 – 18.64)	p > 0.05
LYM (G/L)	0.78 (0.45 – 1.29)	1.00 (0.57 – 1.42)	0.72 (0.44 – 1.17)	p > 0.05
RBC (T/L)	4.03 (3.28 – 4.51)	4.12 (3.39 – 4.58)	4.03 (3.28 – 4.44)	p > 0.05
HGB (g/L)	118 (96 – 132)	123 (101 – 132)	116 (96 – 131)	p > 0.05
HCT (%)	36.5 (30.2 – 40.7)	37.4 (30.5 – 42.7)	36.0 (30.4 – 40.0)	p > 0.05
PLT (G/L)	199 (113 – 270)	210 (136 – 256)	196 (112 – 271)	p > 0.05

Comment:

The median white blood cell count, neutrophil, and lymphocyte count were 14.74, 13.39, and 0.78, respectively. There was no significant difference between the sepsis and septic shock group ($p > 0.05$).

Other values, including hemoglobin, hematocrit, and platelet, were not significantly different between sepsis and septic shock patients ($p > 0.05$).

Table 3.6 Characteristics of biochemistry tests in the study group

Parameter	All	Sepsis (n = 28)	Septic shock (n= 113)	p-value
	Median ***(Interquartile range)***	**Median** ***(Interquartile range)***	**Median** ***(Interquartile range)***	
Creatinine (µmol/L)	173 (113 – 270)	165 (101 – 270)	180 (116 – 260)	p > 0.05
Urea (mmol/L)	13.1 (9.6 – 19.9)	13.0 (7.8 – 18.0)	13.2 (7.8 – 18.0)	p > 0.05
AST (U/L)	49 (30 – 173)	41 (30 – 127)	52 (30 – 188)	p > 0.05
ALT (U/L)	41 (20 – 121)	33 (15 – 96)	41 (22 – 139)	p > 0.05
Total Bilirubin (µmol/L)	19 (12 – 31)	18 (12 – 24)	22 (12 – 31)	p > 0.05
Albumin (g/L)	28.9 (26.0 – 32.0)	31.2 (28.7 – 34.8)	28.6 (25.2 – 31.7)	**p < 0.01**
Procalcitonin (ng/mL)	21 (5 – 99)	16 (6 – 53)	25 (5 – 100)	p > 0.05
Lactate (mmol/L)	3.5 (2.1 – 6.1)	2.9 (1.9 – 4.5)	3.6 (2.2 – 6.4)	p > 0.05

Comment:

There was no significant difference between the sepsis and septic shock group in the median value of creatinine, urea, AST, ALT, bilirubin, procalcitonin, and lactate ($p > 0.05$).

Albumin was the only biochemistry test significantly lower in septic shock patients compared to sepsis patients ($p < 0.05$).

Table 3.7 Blood culture results in the study group

Blood culture	All (n=140)		Sepsis (n = 27)		Septic shock (n= 113)		p value
	n	%	n	%	n	%	
Positive	49	34.3	8	29.6	41	35.4	p > 0.05
Negative	91	65.7	19	70.4	73	64.6	

Comment:

One hundred forty patients had blood culture results, and the positive rate was 34.3%. There was no significant difference in the positive rate between sepsis and septic shock group (p > 0.05).

Table 3.8 Microbial characteristics of positive blood cultures in the study group

Group	Species	Number of patients (n = 49)	Percentage
Gram-negative		41	82.7%
	Escherichia coli	24	49.0%
	Klebsiella pneumonia	11	22.4%
	Pseudomonas aeruginosa	2	4.1%
	Salmonella enterica	1	2.0%
	Bacteroides thetaiotaomicron	1	2.0%
	Moraxella catarrhalis	1	2.0%
	Enterobacter cloacae	1	2.0%
Gram-positive		8	16.3%
	Staphylococcus aureus	3	6.1%
	Streptococcus pneumonia	1	2.0%
	Staphylococcus hominis	1	2.0%
	Staphylococcus haemolyticus	1	2.0%
	Streptococcus intermedius	1	2.0%
	Streptococcus constellatus	1	2.0%

Comment:

Gram-negative bacterial species comprised most of the positive blood cultures. *Escherichia coli* is the most common bacteria, accounting for almost 50% of the cultures.

Within the gram-positive culture, *Staphylococcus aureus* was the most common species.

Table 3.9 Characteristics of severity scoring systems in the study group

Scoring system	All	Sepsis (n = 28)	Septic shock (n= 113)	p value
	Median *(Interquartile range)*	Median *(Interquartile range)*	Median *(Interquartile range)*	
SOFA	10 (8 – 13)	7 (5 – 8)	11 (8 – 13)	**p < 0.01**
APACHE II	20 (16 – 24)	20 (15 – 24)	20 (16 – 23)	p > 0.05
SAPS II	45 (37 – 57)	40 (36 – 45)	48 (38-58)	**p < 0.05**
mNUTRIC	5 (4 – 7)	4 (4 – 6)	5 (4 – 7)	**p < 0.05**

Comment:

Patients who presented with septic shock had a significantly higher median score of SOFA, SAPSII, and mNUTRIC score compared to patients who only presented with sepsis ($p < 0.05$).

However, no difference in APACHE II score was observed between the sepsis and septic shock group ($p > 0.05$).

Table 3.10 Comparison of several clinical features between survivors and non-survivors

Parameter	Survivors (n = 96)	Non-survivors (n= 45)	p-value
Age (year)	69.8 ± 14.3	76.8 ± 12.6	**p < 0.01**
Male sex (n%)	62 (64.6%)	37 (82.2%)	**p < 0.05**
Kidney failure (n%)	62 (64.6%)	38 (84.4%)	**p < 0.05**

CRRT (n%)	30 (31.3%)	29 (64.4%)	**p < 0.01**
Mechanical ventilation (n%)	43 (44.8%)	35 (77.8%)	**p < 0.01**
Positive blood culture (n%)	33 (35.4%)	15 (34.1%)	p > 0.05
Number of comorbidities (X ± SD)	1.48 ± 1.21	2.00 ± 1.26	**p < 0.05**
History of heart failure	5 (5.2%)	7 (15.6%)	**p < 0.05**
History of CKD	8 (8.3%)	11 (24.4%)	**p < 0.05**
SOFA	9 (7 – 12)	12 (10 – 15)	**p < 0.01**
APACHE II	19 (15 – 23)	22 (20 – 24)	**p < 0.01**
SAPS II	42 (32 – 52)	52 (43 - 65)	**p < 0.01**
mNUTRIC	5 (3 – 6)	6 (6 – 7)	**p < 0.01**

Comment:

Compared to survivors, non-survivors were significantly older with a higher rate of kidney failure, requirement for continuous renal replacement therapy, requirement for mechanical ventilation, and higher number of comorbidities ($p < 0.05$).

Male sex was also significantly higher in non-survivors ($p < 0.05$).

The positive rate of blood culture was similar between survivors and non-survivors ($p > 0.05$).

Non-survivors had significantly higher median scores of all calculated scoring systems, including SOFA, APACHE II, SAPS II, and mNUTRIC ($p < 0.05$).

Table 3.11 Comparison of lab features between survivors and non-survivors

Parameter	**Survivors (n = 96)**	**Non-survivors (n= 45)**	**p-value**
WBC (G/L)	14.6 (8.6 – 20.9)	15.2 (11.0 – 20.5)	p > 0.05

NEU (G/L)	13.3 (7.3 – 18.9)	14.4 (9.3 – 18.6)	p > 0.05
LYM (G/L)	0.9 (0.5 – 1.3)	0.6 (0.3 – 0.8)	**P < 0.01**
PLT (G/L)	198 (123 – 260)	212 (86 – 303)	p > 0.05
Creatinine (µmol/L)	168 (109 – 255)	187 (137 – 279)	p > 0.05
Total Bilirubin (µmol/L)	18.4 (12.1 – 30.3)	22 (12.1 – 31.7)	p > 0.05
Albumin (g/L)	29.6 (26.9 – 32.7)	28.3 (24.3 – 31.0)	**P < 0.05**
Procalcitonin (ng/mL)	36.9 (5.7 – 114.6)	11.8 (4.4 – 38.3)	**P < 0.05**
Lactate (mmol/L)	3.1 (1.9 – 5.4)	4.0 (2.8 – 7.1)	**P < 0.05**

Comment:

Non-survivors had significantly lower absolute counts of lymphocyte, albumin, and procalcitonin ($p < 0.05$).

Non-survivors had significantly higher lactate ($p < 0.05$).

There was no significant difference in white blood cell count, absolute neutrophil count, platelet, creatinine, and total bilirubin between survivors and non-survivors ($p > 0.05$).

Table 3.12 Characteristics of treatment outcomes in the study group

Parameter	**All**	**Sepsis**		**Septic shock**		**p-value**
		n	**Median**	**n**	**Median**	
Hospital length of stay (n = 141)	11 (7 – 18)	28	14 (8 – 18)	113	10 (7 – 18)	p > 0.05
Mechanical ventilator days (n = 78)	5 (3 – 8)	11	5 (3 – 6)	67	5 (2.5 – 7.5)	p > 0.05

Comment:

The median number of hospital length of stay and mechanical ventilation days are not significantly different in the sepsis and septic shock groups ($p > 0.05$).

Table 3.13 Mortality rate in the study group

	All (n = 141)	**Sepsis (n = 27)**	**Septic shock (n= 113)**	**p-value**
Mortality	45 (31.9%)	5 (17.9%)	40 (35.4%)	$p > 0.05$

Comment:

The mortality rate of sepsis group is lower than the septic shock group; however, this is not statistically significant ($p > 0.05$).

Table 3.14 Mortality by infection sources in the study group

Source of infection	**All**		**Survivors**		**Non-survivors**		**p-value**
	n	*%*	**n**	*%*	**n**	*%*	
Pulmonary	63	*44.7*	32	*50.8*	31	*49.2*	**p < 0.05**
Gastrointestinal	28	*19.9*	22	*78.6*	6	*21.4*	
Urinary	26	*18.4*	25	*96.2*	1	*3.8*	
Skin and soft tissue	7	*5.0*	4	*57.1*	3	*42.9*	
Others	17	*12.1*	13	*76.5*	4	*23.5*	

Comment:

The highest mortality was observed in the pulmonary source (49.2%). Skin and soft tissue sepsis was also highly fatal (42.9%). Gastrointestinal sources and other sources had a mortality rate of about 20%. Urinary sepsis had the lowest mortality at only 3.8%. The difference was statistically significant ($p < 0.05$).

3.2 CHARACTERISTICS OF NEUTROPHIL TO LYMPHOCYTE RATIO

3.2.1 Neutrophil to lymphocyte ratio and clinical features

All 141 patients had their NLR index calculated on day 1. However, one patient in the sepsis group did not have a complete blood count on day 3 as this patient was stable. Nine

patients in the septic shock group died before day 3. As a result, only 104 NLR index was calculated on day 3 for the septic shock group.

Table 3.15 Neutrophil-to-lymphocyte ratio according to infection severity

Group / Index	Sepsis		Septic shock		p-value
	n	Median	n	Median	
NLR day 1	28	10.80 (7.00 – 18.82)	113	17.55 (9.99 – 26.29)	p = 0.077
NLR day 3	27	13.05 (6.67 – 16.25)	104	18.03 (9.34 – 31.27)	**p = 0.007**

Comment:

Patients with septic shock had higher median NLR on day 1 compared to patients with sepsis; however, this difference was not statistically significant ($p > 0.05$).

On day 3, the median NLR of septic shock patients was significantly higher than that of sepsis patients ($p < 0.05$).

Table 3.16 Neutrophil-to-lymphocyte ratio according to sex

Sex / Index	Male		Female		p-value
	n	Median	n	Median	
NLR day 1	99	16.54 (8.45 – 26.78)	42	14.25 (9.78 – 20.50)	p = 0.353
NLR day 3	90	16.96 (8.71 – 29.38)	41	13.55 (6.71 – 23.86)	p = 0.079

Comment:

Before day 3, nine male patients died, and one female patient did not have their complete blood count taken.

Between males and females, there were no statistically significant differences in NLR on both day 1 and day 3, even though there was a trend toward higher levels in males ($p > 0.05$).

Table 3.17 Neutrophil-to-lymphocyte ratio according to age groups

Age / Index	18 – 65		Above 65		p-value
	n	Median	n	Median	
NLR day 1	43	13.96 (6.73 – 21.75)	98	17.59 (10.05 – 26.57)	p = 0.111
NLR day 3	40	13.26 (6.95 – 20.47)	91	17.16 (8.58 – 30.83)	p = 0.085

Comment:

There were 43 patients between 18 and 65, accounting for 30.5% of the cohort. There were 98 patients above 65 years old (69.5%).

Median NLR on both day 1 and day 3 of patients above 65 was higher, but the differences were not statistically significant ($p > 0.05$).

Table 3.18 Neutrophil-to-lymphocyte ratio according to blood culture results

Group / Index	Positive blood culture		Negative blood culture		p-value
	n	Median	n	Median	
NLR day 1	49	18.15 (11.75 – 29.19)	91	12.76 (8.47 – 23.32)	p = 0.065
NLR day 3	43	20.43 (11.28 – 31.69)	87	15.13 (6.97 – 25.03)	p = 0.062

Comment:

There was a trend toward higher NLR on both day 1 and day 3 for patients with positive blood cultures; however, this was not statistically significant (p > 0.05).

3.2.2 Neutrophil to lymphocyte ratio and treatment outcomes

100 patients (70.9% of the cohort) met the definition for acute kidney injury, according to AKIN criteria.

Table 3.19 Neutrophil-to-lymphocyte ratio according to acute kidney injury

Group / Index	AKI		No AKI		p-value
	n	Median	n	Median	
NLR day 1	100	17.12 (8.95 – 26.67)	41	12.96 (9.99 – 19.73)	p = 0.479
NLR day 3	90	18.03 (11.49 – 31.09)	41	11.49 (6.45 – 20.20)	**p = 0.003**

Comment:

NLR on both day 1 and day 3 were higher in patients with acute kidney injury however, the difference was statistically significant only on day 3 ($p < 0.05$).

Table 3.20 Neutrophil-to-lymphocyte ratio according to the requirement for CRRT

Group / Index	CRRT		No CRRT		p-value
	n	Median	n	Median	
NLR day 1	59	18.89 (11.25 – 33.76)	82	12.01 (8.44 – 21.49)	p = 0.255
NLR day 3	53	22.67 (13.83 – 36.45)	78	13.54 (6.71 – 20.56)	**p < 0.001**

Comment:

Among the patients with acute kidney injury, 59 patients (59% of AKI patients 41.8% of the cohort) required continuous renal replacement therapy.

A similar trend to AKI was observed in patients with CRRT. Patients who required CRRT had higher NLR on both day 1 and day 3, but it was statistically significant only on day 3 ($p < 0.05$).

Table 3.21 Neutrophil-to-lymphocyte ratio according to the requirement for mechanical ventilation

Group / Index	Mechanical ventilation		No mechanical ventilation		p value
	n	Median	n	Median	
NLR day 1	78	14.61 (9.83 – 24.86)	63	16.54 (8.49 – 26.44)	p = 0.461
NLR day 3	70	17.77 (9.98 – 31.61)	61	15.13 (7.23 – 24.10)	p = 0.092

Comment:

78 patients (55.3% of the cohort) required mechanical ventilation support. On both day 1 and day 3, similar NLR was observed for patients with and without mechanical ventilation. There was no significant difference between the two groups ($p > 0.05$).

Table 3.22 Neutrophil-to-lymphocyte ratio according to liver dysfunction

Group / Index	Liver dysfunction (Total bilirubin > 32 µmol/L)		No liver dysfunction (Total bilirubin ≤ 32 µmol/L)		p-value
	n	Median	n	Median	
NLR day 1	31	19.12 (11.03 – 30.73)	110	14.31 (8.50 – 23.02)	p = 0.171
NLR day 3	26	20.29 (13.52 – 35.64)	105	15.13 (7.23 – 26.33)	p = 0.122

Comment:

There were 31 patients (22% of the cohort) who got two points or more on the SOFA scoring system for liver dysfunction.

On both day 1 and day 3, higher medians of NLR were observed in patients with liver dysfunctions.

The differences in NLR between the two groups were not statistically different on both day 1 and day 3 ($p > 0.05$).

Table 3.23 Neutrophil-to-lymphocyte ratio according to in-hospital mortality

Group / Index	Survivors		Non-survivors		p-value
	n	Median	n	Median	
NLR day 1	96	12.13 (8.45 – 20.38)	45	23.02 (12.96 – 35.90)	**p < 0.001**
NLR day 3	95	14.08 (6.75 – 24.10)	36	20.93 (14.76 – 37.92)	**p = 0.002**

Comment:

Before day 3, nine patients died in the non-survivor group. One patient in the survivor group did not have a complete blood count on day 3.

On day 1, non-survivors had a higher median NLR compared to survivors. These two groups' differences were statistically significant ($p < 0.05$).

On day 3, the NLR of the remaining 36 non-survivors remained higher than survivors, and the difference was also statistically significant ($p < 0.05$).

3.3 THE CORRELATION OF NLR AND OTHER PREDICTIVE VALUES FOR SEPSIS SEVERITY AND IN-HOSPITAL MORTALITY

❖ **The correlation of NLR with some prognostic factors of severity:**

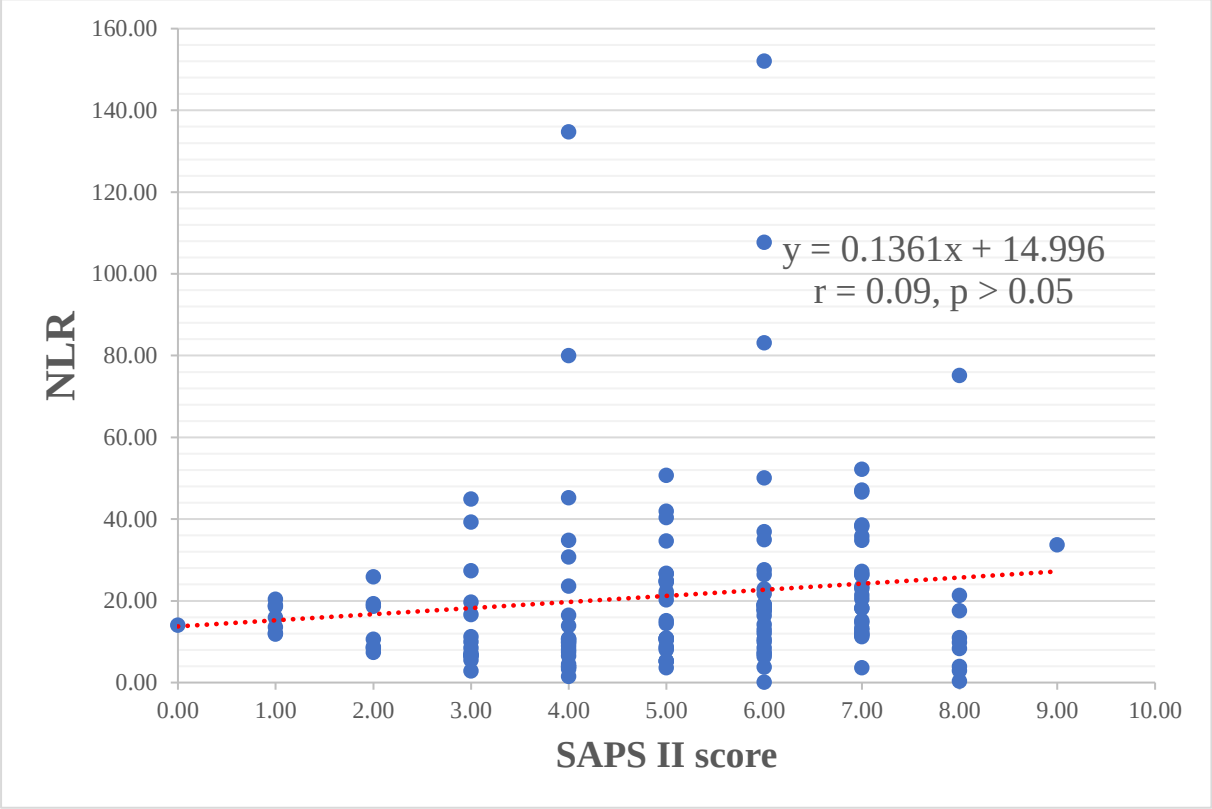


Figure 3.1 Correlation between NLR and SAPS II scores

Comment:

There was a weak correlation between NLR and SAPS II scores with r of 0.09; however, this was not statistically significant ($p > 0.05$).

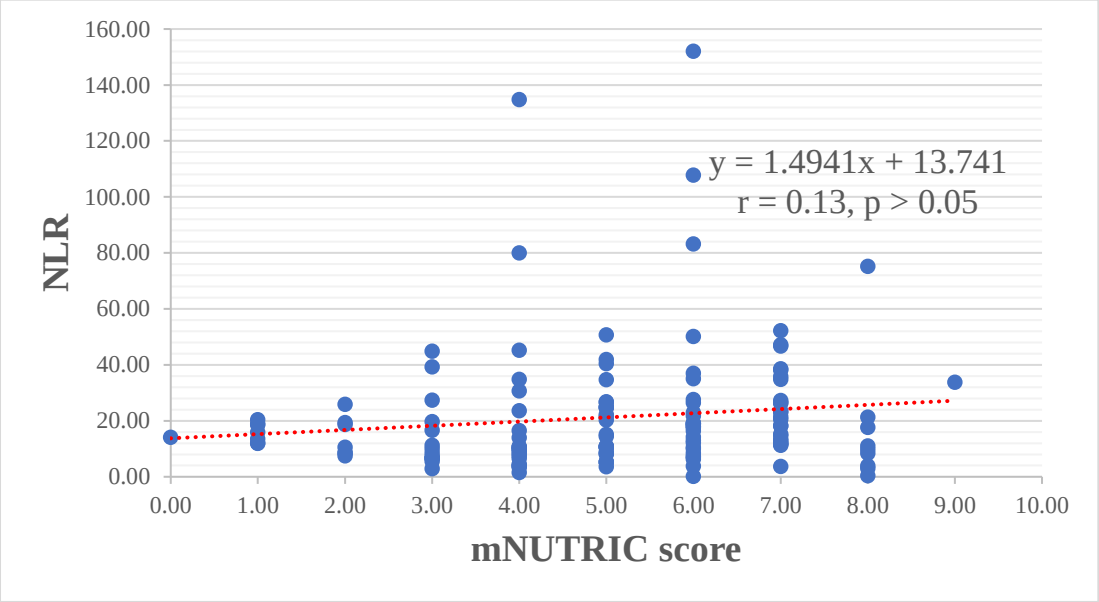


Figure 3.2 Correlation between NLR and mNUTRIC scores

Comment:

There was a weak correlation between NLR and mNUTRIC scores with r of 0.13; however, this was not statistically significant ($p > 0.05$).

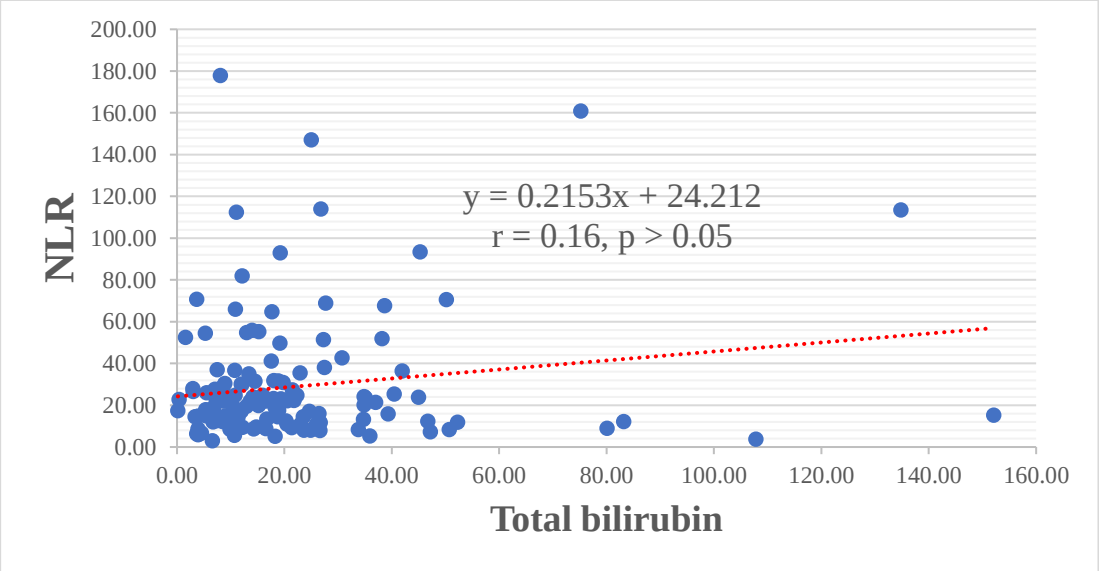


Figure 3.3 Correlation between NLR and total bilirubin

Comment:

There was a weak correlation between NLR and total bilirubin with r of 0.16; however, this was not statistically significant ($p > 0.05$).

3.3.2. The correlation of NLR with mortality in patients with septic shock

Table 3.24 Predictive value for mortality of NLR and severity scoring systems

Predictive value score	Cut-off	Sensitivity	Specificity	AUC	95% CI	p-value
NLR	22.9	51.1%	81.25%	0.68	0.60 – 0.76	**p < 0.01**
SOFA	10	66.7%	65.6%	0.70	0.62 – 0.78	**p < 0.01**
APACHE II	18	82.2%	50.0%	0.65	0.57 – 0.73	**p < 0.01**
SAPS II	39	93.3%	42.7%	0.72	0.64 – 0.79	**p < 0.01**
mNUTRIC	5	75.6%	68.8%	0.77	0.69 – 0.83	**p < 0.01**

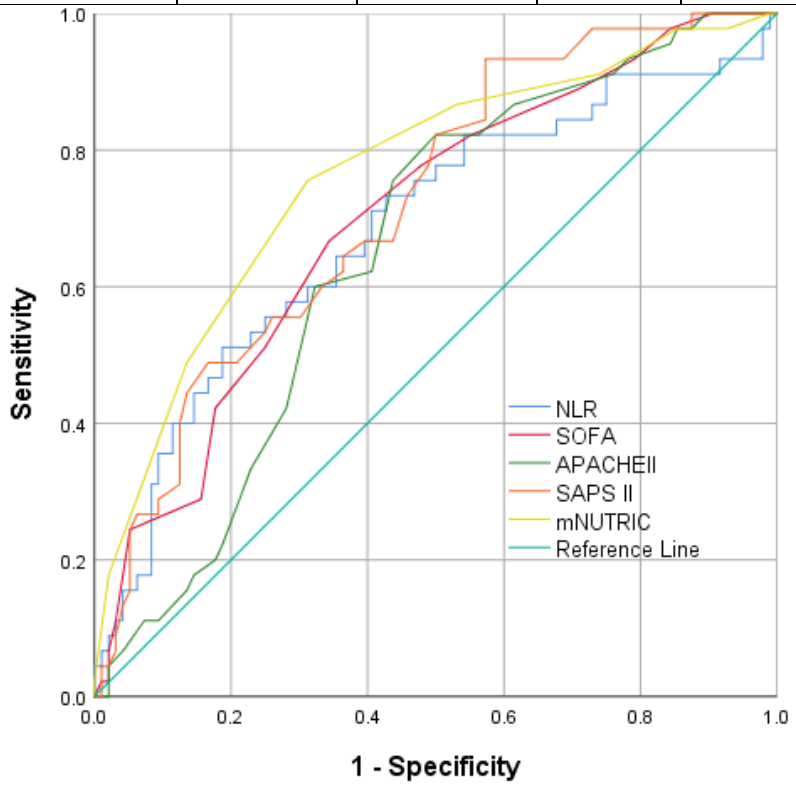


Figure 3.4 ROC curves of NLR and other severity scoring systems in predicting mortality

Comment:

The area under the curve for NLR, SOFA, APACHE II, SAPS II, and mNUTRIC are 0.68, 0.70, 0.65, 0.72, and 0.77, respectively. NLR and all the scoring systems had statistically significant correlations with mortality ($p < 0.05$).

NLR had a higher AUC than APACHE II but a lower AUC than SOFA, SAPS II, and mNUTRIC.

The optimal cut-off values for NLR, SOFA, APACHE II, SAPS II, and mNUTRIC are 22.9, 10, 18, 39, and 5, respectively. With these cut-offs, SAPS II provided the highest sensitivity at 93.3% for mortality, and NLR provided the highest specificity at 81.25%.

Table 3.25 Predictive value for mortality of NLR and some biological markers

Predictive value	Cut-off	Sensitivity	Specificity	AUC	95% CI	P value
NLR	22.9	51.1%	81.25%	0.68	0.60 – 0.76	**p < 0.01**
Age	67	77.8%	46.9%	0.65	0.56-0.72	**P < 0.01**
Lactate (mmol/L)	3.1	71.1%	53.1%	0.62	0.54 – 0.70	**p < 0.05**
Albumin (g/L)	32.4	91.1%	27.1%	0.61	0.53 – 0.69	**p < 0.05**

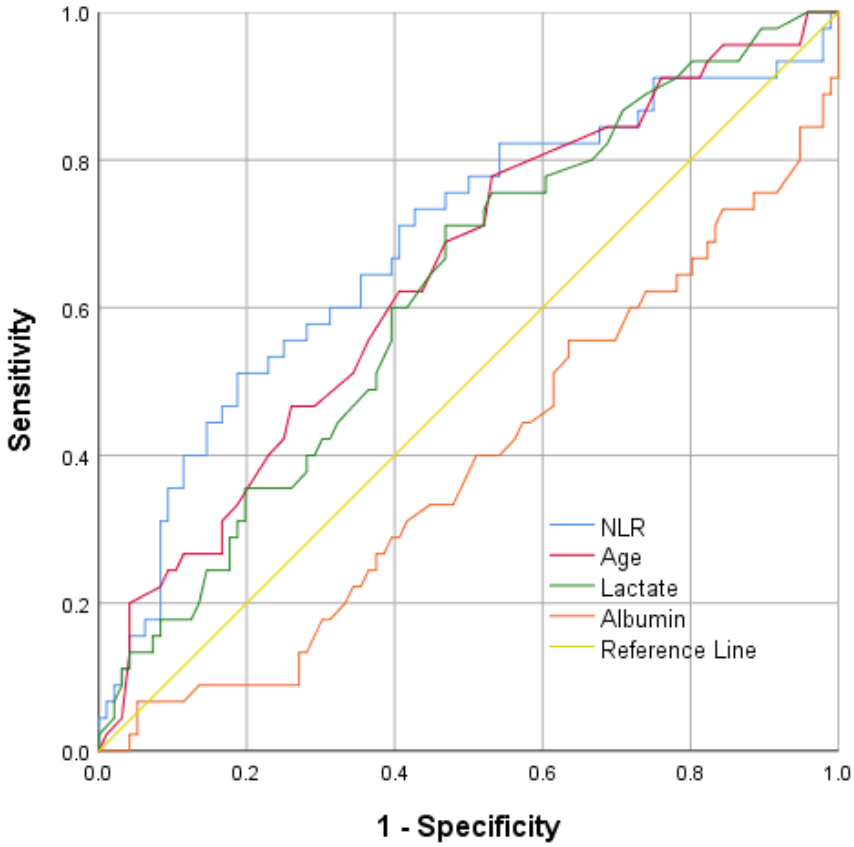


Figure **mortality**

Comment:

The areas under the curve for NLR, age, lactate, and albumin were 0.68, 0.65, 0.62, and 0.61. These values were statistically significant ($p < 0.05$). NLR had higher AUC than age, lactate, and albumin.

Optimal cut-offs for NLR, age, lactate, and albumin were 22.9, 67, 3.1, and 32.4, respectively. With these cut-offs, low albumin had the highest sensitivity of 91.1% for mortality, and NLR had the highest specificity of 81.25%.

Table 3.26 Predictive value for mortality when combined with NLR and the severity scoring systems

Predictive value	AUC	95% CI	p-value
NLR	0.68	0.60 – 0.76	$p < 0.01$
NLR + SOFA	0.75	0.66 – 0.83	$p < 0.01$
NLR+ APACHE II	0.73	0.64 – 0.81	$p < 0.01$
NLR + SAPS II	0.77	0.69 – 0.85	$p < 0.01$
NLR + mNUTRIC	0.81	0.73 – 0.89	$p < 0.01$

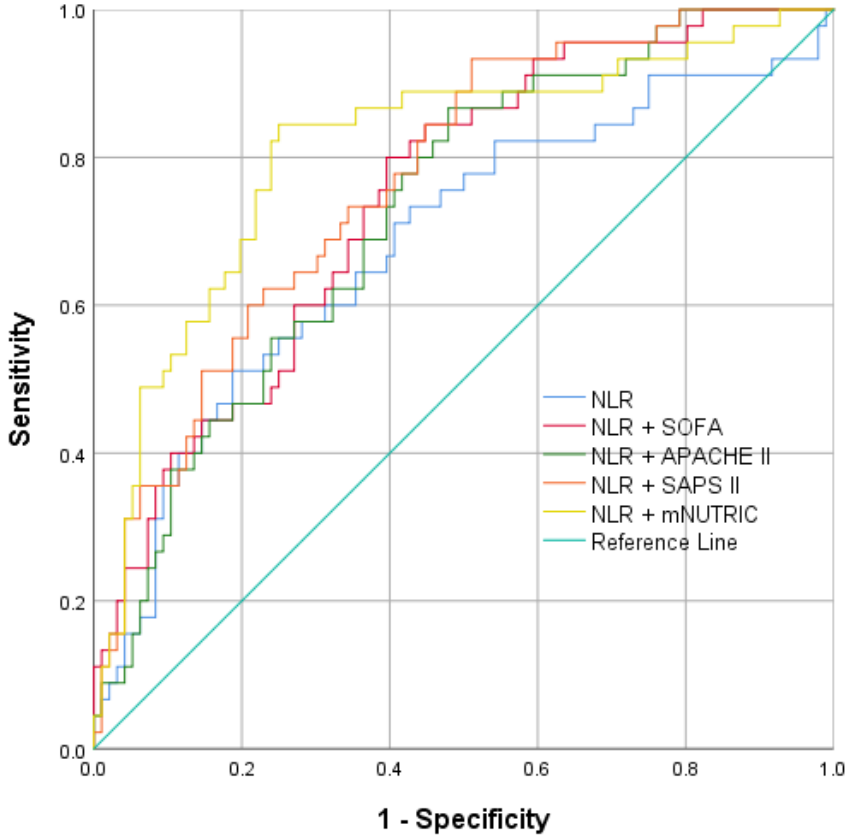


Figure 3.6 ROC curves of the severity scoring systems in combination with NLR for predicting mortality

Comment:

When combined NLR with the severity scoring systems, the AUC increased to 0.75, 0.73, 0.77, and 0.81 for SOFA, APACHE II, SAPS II, and mNUTRIC, respectively. All the values were statistically significant ($p < 0.05$).

Table 3.27 Comparison of AUCs of NLR and other severity markers

Predictive value	NLR (AUC = 0.68)
SOFA (AUC = 0.70)	$p > 0.05$
APACHE II (AUC = 0.65)	$p > 0.05$
SAPS II (AUC = 0.72)	$p > 0.05$
mNUTRIC (AUC = 0.77)	$p > 0.05$
Lactate (AUC = 0.62)	$p > 0.05$
Albumin (AUC = 0.61)	$p > 0.05$

Comment:

There was no significant difference between the AUC of NLR and the AUCs of other severity scoring systems and biological markers ($p > 0.05$).

Table 3.28 Univariate analysis of sepsis mortality for variables in this study

Parameter	OR	95% CI	p-value
Age	1.04	1.01 – 1.07	**p < 0.01**
Male sex	2.54	1.06 – 6.06	**p < 0,05**
AKI	2.98	1.20 – 7.38	**p < 0,05**
CRRT	3.99	1.89 – 8.42	**p < 0.01**
Mechanical ventilation	5.14	2.23 – 11.85	**p < 0.01**
Number of comorbidities	1.43	1.07 – 1.91	**p < 0,05**
SOFA	1.24	1.10 – 1.38	**p < 0.01**
APACHE II	1.08	1.02 – 1.14	**p < 0,05**
SAPS II	1.06	1.03 – 1.10	**p < 0.01**
mNUTRIC	1.85	1.41 – 2.42	**p < 0.01**
NLR	1.03	1.01 – 1.05	**p < 0.01**
Lymphocyte count	0.43	0.22 – 0.86	**p < 0,05**
Albumin	0.90	0.83 – 0.98	**p < 0,05**
Lactate	1.11	1.01 – 1.22	**p < 0,05**

Comment:

In our univariate analysis, a point increase in NLR increased mortality by 3%. Each year of age increased mortality by 4%. One additional comorbidity increased mortality by 46% ($p < 0.05$).

Each point increase in SOFA, APACHE II, SAPS II, and mNUTRIC increased mortality by 24%, 8%, 6%, and 85%, respectively ($p < 0.05$).

Patients who suffered from AKI, required CRRT, or required mechanical ventilation had their mortality increased 3-fold, 4-fold, and 5-fold, respectively ($p < 0.05$).

Males were 2.54 times more likely to die compared to females ($p < 0.05$).

Each point increase in absolute lymphocyte count and albumin decreased mortality by 57% and 10%, respectively ($p < 0.05$).

Each point increase in lactate increased mortality by 11% ($p < 0.05$).

Table 3.29 Multivariate analysis of mortality in this study

Parameter	OR	95% CI	p value
Age	1.03	0.99 – 1.06	p > 0.05
Male sex	1.78	0.63 – 5.06	p > 0.05
AKI	1.86	0.58 – 5.98	p > 0.05
Mechanical ventilation	4.28	1.39 – 13.21	**p < 0.05**
Number of comorbidities	1.39	0.97 – 1.98	p > 0,05
SOFA	1.11	0.94 – 1.30	p > 0,05
NLR	1.03	1.01 – 1.06	**p < 0.01**
Lactate	1.04	0.92 – 1.17	p > 0,05

Comment:

In our multivariate analysis of NLR and other variables, NLR and the need for mechanical ventilation maintained their statistically significant predictive value for sepsis mortality ($p < 0.05$). Specifically, each point increase in NLR increased mortality by 3%, and the need for mechanical ventilation increased mortality by over 4 times.

Over variables including age, sex, AKI, number of comorbidities, and lactate did not have a statistically significant predictive value for sepsis mortality ($p > 0.05$).

CHAPTER 4. DISCUSSION

4.1 THE GENERAL CHARACTERISTICS OF STUDY POPULATION

❖ **Sex, age, and number of comorbidities of the participants:**

The mean age of our participants was 72 years old, with a standard deviation of 14.1 years. The mean age of sepsis patients was 75.3±12.3, and the mean age of septic patients was 71.2±12.3. There was no significant difference in the mean age of sepsis and septic shock group. Most of our patients were male (70.2%), which accounted for 71.4% of sepsis patients and 69.9% of septic shock patients. Our participants had a mean of 1.62 comorbidities. The number of comorbidities ranged from 0 to 5 diseases.

Our participants' mean age was slightly higher than in previous research. Male patients disproportionately dominated our study cohort. For example, an epidemiology study in the United States recorded over four million patients with sepsis from 1995 to 2000 and found a mean age of 60.8 and a standard deviation of 13.7. Moreover, the number of male patients was only 48%.[19]

A later study from 2011 to 2015 in England reported a mean age of 63.3±16.9 for sepsis patients and a mean age of 65.3±15 for septic shock patients. In this study, male patients accounted for 55% of sepsis patients and 55.4% of septic shock patients.[53]

As previously stated, there was a trend toward increasing incidence in the older population, and our study population was years later than the previously mentioned research. In addition, 108 Central Military Hospital is one of the largest tertiary care hospitals in Northern Vietnam. As a result, several of our participants were referred from other primary or secondary care centers, and these patients tended to be older and more severe. These reasons can partly explain the higher mean age of our cohort. Because our cohort was mainly male patients, our results may not represent female patients with sepsis well.

Most of our participants had one or two comorbidities. With so many chronic illnesses emerging, we believed a mean of 1.62 comorbidities could represent the overall population.

❖ **Clinical characteristics:**

Only 31 of our participants (22%) had no comorbidities. The three most common chronic illnesses in our cohort were hypertension (75 patients, 53.2%), diabetes (50 patients, 35.5%), and stroke (28 patients, 19.9%). The distribution of comorbidities in the sepsis and septic shock group was similar.

A systematic review of the prevalence of hypertension in the Vietnamese population found a pooled prevalence of 21.1%, which was much lower than the prevalence of hypertension in our cohort.[54] However, in a study in China on 7071 sepsis patients, the prevalence of hypertension was 56.2%, which was similar to our cohort.[55] This result might suggest that patients with hypertension were more prone to developing sepsis.

Diabetes has been known to alter several aspects of our immune system and is a known risk factor for infection and sepsis.[56] For patients with sepsis, the prevalence of diabetes increased from 12.2% in the 1979-1984 period to 18.7% in the 1995-2000 period in the United States.[19] A nationwide Swedish study also recorded a prevalence of 22.5% in sepsis patients. Moreover, in their multivariate logistic regression model, patients with diabetes had an odd ratio of 1.98 for developing sepsis if they had no diabetes complications and an odd ratio of 2.65 if they had diabetes complications.[57] In a recent study on patients with sepsis in Northern Vietnam from 2016-2018, a prevalence of 25.3% for diabetes was recorded.[24] Our cohort had a higher prevalence of diabetes compared to those in the study. Compared to the national prevalence of diabetes in Vietnam, which was reported at 5.4% in 2012, our cohort had a much higher prevalence of 35.5%.[58] It showed that diabetes is an important risk factor for sepsis.

In the previously mentioned Swedish study, the researchers also reported a prevalence of 13% for cerebrovascular diseases in sepsis patients and an odd ratio of 1.7 in developing sepsis.[57] This number was lower than our recorded stroke prevalence in the cohort, which was 19.9%.

Due to the similar distribution of comorbidities between the sepsis and septic shock group, no comorbidity in our study increased the likelihood of developing septic shock in patients with sepsis.

- **Characteristics of infection sources:**

Pulmonary infection was the most relevant in our study, with 44.7% of patients. Gastrointestinal infections and urinary infections were similar, and each of them accounted for 20% of patients. A similar distribution was observed in sepsis and septic shock patients. According to the Global Burden of Disease Study, diarrheal diseases have been the leading cause of sepsis since 1990 up until 2017. Lower respiratory infections were the second leading cause of sepsis, and urinary infections were among the top ten causes.[20] A study in English from 2011 to 2015 on over 200.000 patients showed that respiratory infections accounted for 50.1% of sepsis cases and 42.1% of septic shock cases. Gastrointestinal infections were also highly prevalent, with 25.8% of sepsis patients and 31.4% of septic shock patients. However,

genitourinary only accounted for 6.5% of sepsis patients and 6.1% of septic shock patients.[53] Our study closely resembled this distribution; however, we did not observe any case of neurological infection. In 108 Central Military Hospital, central nervous infection was treated in a different ward, which could explain why we did not observe any cases of meningitis and encephalitis.

In Southeast Asia, respiratory infection was also the most common clinical presentation of sepsis, accounting for 53% of cases in adult patients. Other common causes reported were diarrhea and central nervous system infection. In addition, several viruses were identified as the cause of sepsis. The most prevalent virus was dengue, which accounted for 8% of cases.[59] A paper reported findings on infectious foci in sepsis from various studies, and the majority of these studies found that respiratory infection was the leading cause of sepsis.

In conclusion, our study cohort closely resembled the infection distribution from other studies in Europe and Southeast Asia. The most common infection source for sepsis was pulmonary. However, our population lacked several important causes of sepsis, including viruses and central nervous systems. Our result cannot be applied to central nervous system infection and viral causes.

- **Hemodynamic characteristics and lab test features:**

The median mean blood pressure of our cohort was 77mmHg. Even though all patients in the septic shock group received appropriate vasopressor doses, their median mean blood pressure was significantly lower than that of sepsis patients, as expected. Similar differences were observed in systolic blood pressure and diastolic blood pressure. The median heart rate for the cohort was 110 beats per minute. The difference was insignificant in the heart rate, which was slightly higher in septic shock patients.

Our study's median white blood cell count, neutrophil count, and lymphocyte count were 14.74 G/L, 13.39 G/L, and 0.78 G/L, respectively. There was a trend toward higher white blood cell count, higher neutrophil count, and lower lymphocyte count, but none were statistically significant. A study of critically ill patients reported a median of 8.9 for the entire cohort and 10.9 for their sepsis subgroup.[44] Another sepsis patient study found a median white blood cell count around 13.4 – 13.6 G/L, which was more approximate to our cohort.[60] In 373 sepsis patients in Turkey, the median white blood cell count, neutrophil count, and lymphocyte count were 12.8, 9.0, and 1.3, respectively.[42] A retrospective cohort study on the diagnostic value of NLR for sepsis reported a median WBC count at 12.7 G/L, a median neutrophil count at 11.4 G/L, and a median lymphocyte count at 0.7 G/L.[61] Our participants had a higher median

of WBC count, neutrophil count, and a similar median of lymphocyte count compared to previous studies.

Our participants' median hemoglobin was 118 g/L. This result showed that most patients fall into the anemia category, defined as 130-142 g/L in males and 116-123 g/dL in females.[62] Our result was similar to a study in China in which the authors reported a mean hemoglobin of 124 g/L.[63] Another prospective multicenter European study reported a mean hemoglobin of 113 g/L.[64] This phenomenon was commonly observed in critically ill patients. In 1996, a paper from Belgium reported an inappropriately low level of erythropoietin in critically ill patients, especially sepsis patients.[65] Median platelet count in our cohort was 210 G/L for sepsis patients and 196 G/L for septic shock patients. The difference was not statistically different. A mean platelet count value of 228 G/L was found in 145 sepsis patients in Uganda, similar to our study. In this study, a subgroup analysis showed a significantly lower mean platelet count value among patients with severe sepsis compared to patients with sepsis (204.5 G/L vs 264 G/L).[66] A more recent study in Germany with 361 patients reported a platelet count median of 176 G/L. This number was lower than in our study. However, the mortality rate in this study was 52.2%, which might mean that their cohort was more severe than ours.[67] Our results were similar to those of a multicenter study in Vietnam. The authors reported WBC, PLT, and HGB at 15.73 G/L, 185.98 G/L, and 111.4 g/L.[68] This showed that even though our result was in a single center, it somewhat represented the Vietnamese population.

In our study, patients' mean creatinine, AST, and ALT values were 173 µmol/L, 49 U/L, and 41 U/L, respectively. This closely resembled the findings in the previously mentioned German study, which reported a median creatinine of 160 µmol/L, an AST of 56.5 U/L, and an ALT of 31 U/L. Almost 70% of our patients had a creatinine level above 120 µmol/L, which possibly brought them into the acute kidney injury group. However, liver enzymes were only slightly elevated. Our patients' median total bilirubin, procalcitonin, and lactate were 19 µmol/L, 21 ng/mL, and 3.5 mmol/L. All of them were higher than the German study's cohort, which reported these values at 15.4 µmol/L, 2.6 ng/mL, and 2 mmol/L.[67] All previously mentioned biochemistry tests did not differ significantly between sepsis and septic shock groups.

The median albumin of the cohort was 28.9 g/L. Our result was similar to a study on 336 patients in Japan in 2019. In this study, the authors reported a mean albumin level of 28.4 g/L (±0.74).[69] There was a significant difference between the sepsis and septic shock group. Patients with septic shock had a median value of albumin at 28.6 g/L, while patients with sepsis

had a median value of albumin at 31.2 g/L. Low albumin level was associated with higher mortality as well as severity of sepsis.[69–71]

❖ **Characteristics of blood culture:**

Our study had 49 positive blood culture results, accounting for 34.3% of the cohort. The positive rate of blood culture was 29.6% in the sepsis group and 35.4% in the septic shock group. A systematic review, which identified seven studies comprising 22 655 patients, reported a pooled positive rate for culture was 40.1%. However, there was a large difference in the positive rate of culture among the seven studies.[72] In the sub-analysis of Prehospital Antibiotics Against Sepsis trial, 42.6% of patients were identified as culture-positive.[73] In general, our study had a slightly lower rate of culture-positive patients. This might partly be because 108 Central Military Hospital blood cultures were often taken in the intensive care unit after antibiotics were administered in the emergency department.

In our study, 82.7% of positive culture results were gram-negative organisms. The most common causes of sepsis in our cohort were *Escherichia coli* (49%), *Klebsiella pneumonia* (22.4%), and *Staphylococcus aureus* (6.1%). According to a large prospective nationwide cohort study in Japan on causative pathogens in sepsis, the three most common reported pathogens were E. coli, K. pneumonia, and MSSA. However, E. coli, K. pneumonia, and MSSA only accounted for 21.5%, 9%, and 6.5% of 1352 isolated causative pathogens, respectively.[74] This was because they had many other viruses as well as fungi in their study. In Thailand, a study on causative pathogens for sepsis was published in 2014, and their results had a similar distribution to ours. First, 83.7 percent of their isolates were gram-negative. Second, E. coli (44%) and K. pneumonia (19%) were the most common among their gram-negative isolates. Finally, *S. aureus* was still in the top 5 gram-positive pathogens even though it was not the most common.[75] However, a study published in JAMA recorded culture results from many hospitals across 10 states in the United States and found a different distribution of sepsis pathogens. In their study, *E. coli* was still the most common pathogen (13.8%); however, the second most common pathogen was *S. aureus* (11.2%). Other common pathogens reported in this study were *Streptococcus* spp (9%), *K. pneumonia* (5.2%), and *Pseudomonas aeruginosa* (3.9%).[76]

In Southeast Asia, our result was similar to other large studies, showing that gram-negative pathogens were the most common causative agents for sepsis. The gram-negative pathogens were E. coli and K. pneumonia, while the gram-positive pathogen was *S. aureus*. However, this result differed from other regions like the United States, where gram-positive pathogens accounted for much more. This might be due to the overuse of antibiotics in our

region, which can alter bacterial distribution. Many gram-negative species had become more virulent and more resistant to different groups and antibiotics.

❖ **Characteristics of severity:**

In our study, the median SOFA score for the cohort was 10. The median for APACHE II, SAPS II, and mNUTRIC scores were 20, 45, and 5, respectively. The nationwide sepsis study in Japan showed a median SOFA score ranging from 8-10, depending on infection sources. Their APACHE II score also ranged from 21 to 26.[74]. Another national database record from England showed a mean APACHE II score of 18.5 for sepsis and 22 for septic shock patients.[53] In Vietnam, a study at Can Tho Central General Hospital from 2016 to 2018 reported a mean APACHE II score of 22 and a mean SOFA score of 10.1.[23]. An earlier study in 108 Central Military Hospital on 194 intensive care unit patients from 2016 to 2018 reported similar median scores for SOFA (10 points), APACHE II (18 points), SAPS II (44 points), and mNUTRIC (5 points).[24] Moreover, a multicenter study in Vietnam with 252 patients from 15 ICUs reported a median SOFA score of 7 and a median APACHE II score of 18. However, the mortality in this study was 40.1%.[68] Our study population had higher SOFA scores and APACHE II scores, but our mortality was only 31.9%.

Statistical differences in SOFA, SAPS II, and mNUTRIC were seen between sepsis and septic shock groups but not APACHE II. Both sepsis and septic shock patients had a median APACHE II score of 20. Septic shock patients had higher SOFA, SAPS II, and mNUTRIC scores at 11, 48, and 5, while sepsis patients' scores were 7, 40, and 4, respectively ($p < 0.05$). The APACHE II score does not consider the use of vasopressors or inotropes. Some values, like sodium, potassium, temperature, and hematocrit, are not well correlated with the severity of infection. This might explain why we could not see a significant difference between the two groups. On the other hand, a study in China found a significant difference between APACHE II in different severity of sepsis. Liu et al. reported an APACHE II score of 8 (IQR: 5.00-11.50) for sepsis patients, 13 (IQR: 9.00-19.00) for severe sepsis, and 21.5 (IQR: 14.75-30.25).[77]

❖ **Mortality of sepsis and septic shock:**

In our cohort, the overall mortality was 31.9%. The specific mortality for patients with sepsis was 17.9%, and patients with septic shock were 35.4%. Even though we observed a higher mortality in the septic shock group, the low number of patients within the sepsis group made the difference not statistically different ($p > 0.05$). Our study population had lower mortality compared to a multicenter study in Vietnam. They reported a mortality rate of 40.1%. This result was surprising as in this study, their population had lower SOFA score, lower

APACHE II score, and lower percentage of septic shock patients (29.4%).[68] 108 Central Military Hospital is the largest military hospital in the North, and the ICU in this hospital is more well-equipped than other ICUs in Vietnam. In addition, personnel are also more well-trained. This might partly explain the better outcome in this ICU compared to others.

A large study in China with 5357 sepsis patients reported a 28-day mortality rate of 29.29% and a 60-day mortality rate of 33.92%.[71] In Japan, a mortality rate of 23.4% was reported in the nationwide prospective study.[74] In Sweden, a nationwide study reported a 30-day mortality rate of 26.6%; however, they were studying patients with community-acquired sepsis.[57] Many researches have shown a mortality rate at around 20% to 40%, with higher mortality in septic shock. Our result was similar to previous studies. A systematic review of sepsis mortality in Europe, North America, and Australia reports a mortality rate of 34.7% with 170 studies included.[21] This result showed that our mortality rate was also comparable to developed countries in Europe, North America, and Australia. In addition, another systematic review in Korea showed a mortality rate of 28.1% for sepsis and 34.3% for septic shock.[78] This was also within the expected range. Even though we did not observe a statistically significant difference in mortality between sepsis and septic shock patients, septic shock had been known to be associated with increased mortality.[6] A study in Germany on 361 patients reported sepsis mortality of 36.9%, while septic shock mortality was significantly higher at 64.5%.[67]

There was no statistically significant difference between hospital length of stay and mechanical ventilation days. Patients with sepsis required a median hospital length of stay of 14 days and median mechanical ventilation days of 5 days. Patients with septic shock required a median hospital length of stay of 10 days and median mechanical ventilation days of 5 days. In the United States, the median hospital length of stay was found to be 8.6 days for severe sepsis and 10.9 for septic shock. The mean mechanical ventilation days were also found to be 6.6 days.[79]

- **Clinical features related to mortality:**

When comparing 96 survivors and 45 non-survivors, we identified multiple clinical features that were statistically significantly different. Higher age and male sex were correlated with mortality. The mean age of non-survivors was 76.8 ± 12.6, and the mean age of survivors was 69.8 ± 14.3. This was expected because age was a known risk factor for sepsis mortality, especially for those over 65. A national hospital discharge data study with over 10 million patients found an excellent correlation between older age and a higher mortality rate. They reported that patients above 65 were 2.2 times more likely to die from sepsis.[26] Male comprised

64.6% of survivors and 82.2% of non-survivors. A study with 2065 patients reported lower 30-day mortality in females; however, the authors found that female patients had a lower number of comorbidities, were more likely to have urinary tract infections, and had lower severity of diseases. As a result, their multivariate analysis showed that sex was not an independent factor of mortality.[80] researchers were exploring the relationship between sex and sepsis mortality, and several of them also found that male had a higher mortality rate. A retrospective cohort study in Japan used multivariable Cox proportional hazard analysis and found a hazard ratio of 0.74 (95% CI: 0.58-0.88) for female in-hospital sepsis mortality. However, this study's study population was sepsis patients after trauma.[81] A smaller study in Pakistan comparing the mortality and IL-6 levels in males and females found that male patients had a 70% greater mortality rate and higher IL-6 plasma levels.[82] On the other hand, some studies concluded that there was no relationship between sex and mortality. A meta-analysis included 13 studies, and 80 520 patients reported no sex-based differences in all-cause hospital mortality.[83]

In our study, other features that significantly correlated to patients' mortality were acute kidney injury, the need for continuous renal replacement therapy, and the need for mechanical ventilation. As stated in the definition of sepsis, it is a condition in which organ dysfunction occurs due to a systemic response to infection. The kidney and lungs are two major organs affected by sepsis. AKI and CRRT are a continuum of kidney failure severity, while mechanical ventilation support represents severe respiratory dysfunction. Not surprisingly, the presence of these conditions correlated to sepsis mortality. In survivors, the percentages of AKI, CRRT, and mechanical ventilation needs were 64.6%, 31.3%, and 44.8%, respectively. In non-survivors, these percentages were significantly higher at 84.4%, 64.4$%, and 77.8%. In a multicenter study collecting data from the Australian New Zealand Intensive Care Society Adult Patient Database, 42.1% of sepsis patients had concomitant acute kidney injury.[84] A study using a large regional population-based database in Beijing city in China reported the presence of AKI in 48.1% of sepsis patients.[85] Higher mortality was observed in patients with AKI (41.67%) compared to patients without AKI (10.00%).[86] Our rate of AKI was much higher, so it might indicate that our population was on the more severe end of sepsis. Electronic health record data from 28.747 patients with sepsis showed that only 13.5% required mechanical ventilation.[87] However, another study in China with 5 783 patients reported the rate of mechanical ventilation at 48.1%, which was quite similar to our result.[88]

Both survivors and non-survivors in our study had similar rates of positive culture. 35.4% of survivors and 34.1% of non-survivors had positive blood cultures. There was no

difference between the two groups. Similar to our result, a meta-analysis found that about 40.1% of patients with sepsis or septic shock had positive blood cultures, and the blood culture result was not associated with mortality.[72] Another meta-analysis published in 2023 found an all-cause mortality rate of 38.3% in the culture-positive group and 21% in the culture-negative group. However, this difference was not statistically significant (p=0.23), and there was a consequential heterogeneity among the studies.[89] In general, culture results did not correlate with sepsis mortality. This was noteworthy as we thought blood culture results could aid the treatment of sepsis and septic shock. This result stressed the importance of appropriate antibiotic choice in early treatment of sepsis and septic shock as the blood results did not alter the mortality rate.

We also found that the number of comorbidities, history of heart failure, and history of chronic kidney disease were statistically significant differences between survivors and non-survivors. Survivors had a mean number of comorbidities of 1.48 ± 1.21, a lower rate of heart failure (5.2%), and a lower rate of CKD (8.3%). Non-survivors had a mean number of comorbidities of 2.00 ± 1.26, 15.6% of patients with heart failure and 24.4% of patients with CKD. A retrospective cohort study on hospital discharge databases from 2004 and 2007 concluded that the Charlson Comorbidity Index (CCI) was a significant and independent risk factor of hospital mortality.[90] Higher mortality rates in patients with heart failure have been reported in several studies. For example, Dagher et al. reported a higher mortality in sepsis patients who had heart failure (57.5%) compared to patients who did not have heart failure (34.5%).[91] Chronic kidney disease was also reported as a risk factor for mortality in sepsis patients. A study in 2015 looking at CKD and other comorbidities found that CKD had the highest hazard ratio (HR=2.25, 95% CI: 1.46-3.46) after adjusting for relevant confounders.[92]

Even though the APACHE II score was not significantly different between the sepsis and septic shock groups, its' value in predicting mortality was maintained. All four scoring systems were higher in non-survivors. SOFA, APACHE II, SAPS II, and mNUTRIC scores of survivors were 9, 19, 42, and 5, respectively, while the same scores of non-survivors were 12, 22, 52, and 6, respectively. The differences were all statistically different ($p < 0.01$). SOFA has been validated in multiple studies across the globe in predicting sepsis mortality. It is the most used tool to quantify the severity of sepsis. An extensive systematic review found an increase of 2.4% in sepsis mortality for each point increase in SOFA score.[21] A study in Korea with 281 patients also found a lower median value for SOFA in survivors (median = 7, IQR: 5-10) compared to non-survivors (median=10, IQR: 5-15).[93] APACHE II on admission was also found

to be higher in non-survivors in a study from India in 2023. Elangovan et al. reported that the mean value for SOFA and APACHE II on admission of survivors was 6.94 (±3.16) and 16.59 (±8.24). Non-survivors had significantly higher SOFA and APACHE II scores at 9.32 (±3.81) and 23.8(±11.65).[31] SAPS II was also tested in a prospective cohort study and found to be significantly higher in non-survivors. In this study, the mean SAPS II for survivors was 41.75±14.15 while the mean score for non-survivors was 56.5±14.84.[94]

❖ **Lab features related to mortality:**

In non-survivors, the median white blood cell count, neutrophil count, and platelet count were 15.2 G/L, 14.4 G/L, and 212 G/L, respectively. These values were higher than survivors, 14.6 G/L, 13.3 G/L, and 198, respectively. However, there was no statistically significant difference between the two groups in WBC, Neutrophil count, and platelet. Non-survivors had a significantly lower lymphocyte count (median 0.6, IQR: 0.3-0.8) compared to survivors (median 0.9, IQR: 0.5-1.4) ($p < 0.05$). A study in China reported in non-survivors a higher value for WBC count (18.40 G/L vs 15.35 G/L, $p < 0.05$), a higher value for neutrophil count (16.35 G/L vs 12.30 G/L, $p < 0.05$), lower lymphocyte count (0.61 G/L vs 0.84 G/L, $p < 0.05$), and similar platelets count compared to survivors.[77]

We also found that patients in the survivor group had significantly higher albumin level (29.6 g/L vs 28.3 g/L, $p < 0.05$), and lower lactate level (3.1 mmol/L vs 4.0 mmol/L, $p < 0.05$). Interestingly, we observed a significantly higher level of procalcitonin in survivors (36.9 ng/mL vs 11.8 ng/mL, $p < 0.05$). The two groups had no statistically significant difference in creatinine and total bilirubin. A study on the Chinese population also showed similar results with higher albumin level (34.24 g/L vs 30.04 g/L, $p < 0.05$) and lower lactate (1.8 mmol/L vs 2.3 mmol/L, $p < 0.05$) in survivors of sepsis. In this study, procalcitonin was not different between survivors and non-survivors.[77] A study in Japan also found the same results as ours. Their study observed lower albumin level and higher lactate in non-survivors. They did not find statistically significant differences in total bilirubin and creatinine between survivors and non-survivors. They concluded an odd ratio of 3.243 in predicting mortality for hypoalbuminemia in patients with sepsis.[69] With the large public database, Cao et al. developed multiple models to find the relationship between albumin and mortality. They concluded that with albumin of less than 2.6 g/dL, each 1 g/dL increase in albumin decreased the risk of 28-day mortality by 59% and the risk of 60-day mortality by 62%.[71] Lactate is a marker for tissue perfusion, so it can partly represent the severity of sepsis. Higher lactate shows a lack of tissue perfusion, and higher mortality is expected. In our study, most sepsis patients with urinary sources survived, and their

initial procalcitonin was high (median 64.3, IQR: 15.7-132.6). This skewed the procalcitonin and made the procalcitonin level significantly higher in survivors.

❖ **Mortality by infection sources:**

We observed a very high mortality rate in patients with sepsis from pulmonary or skin and soft tissue sources. 49.2% of patients with pulmonary source died, as well as 42.9% of patients with skin and soft tissue sepsis. Gastrointestinal sepsis and other sources carried a mortality rate of 21.4% and 23.5%, respectively. Urinary sepsis had the lowest mortality of only 3.8%. A study from China published in The Lancet reported the mortality rate of different infection sources. The mortality rates for UTIs, gallbladder/bile duct infections, pulmonary infections, enterogenous infections, and SSTIs were 18.53%, 24.01%, 52.55%, 45%, and 30.22%, respectively.[95] These results agreed with ours about the high mortality for pulmonary sepsis and low mortality for UTIs sepsis. However, a study with 3 958 patients in the United States reported very different mortality rates. Their results showed a mortality rate of 18.9% for abdominal sepsis, 19.3% for pulmonary sepsis, and 12.8% for renal sepsis.[96] This result might suggest that there is significant heterogeneity in the mortality rate of different infection sites by region.

4.2 THE CHARACTERISTICS OF NEUTROPHIL TO LYMPHOCYTE RATIO

4.2.1 Neutrophil to lymphocyte ratio and clinical features

In our study, the median NLR for sepsis patients were 10.8 on day 1 and 13.05 on day 3. This was lower than the median NLR for septic shock patients, which were 13.05 on day 1 and 18.03 on day 3. However, this difference was only statistically significant on day 3. A study in Indonesia found a significantly different mean value of NLR between sepsis patients (18.11±1.35) and septic shock patients (20.10±2.89).[97] Another study in Romania also found a statistically significant difference in NLR between sepsis patients (9.15±2.21) and septic shock patients (10.31±2.32). These values, however, were lower than our results. Liu et al. reported significant difference values for NLR with different severity of sepsis. In this study, the median NLR for sepsis patients was 11.11 (IQR: 6.98-18.24), for severe sepsis patients was 22.67 (IQR: 12.35-31.89), and septic shock patients was 31.50 (IQR: 22.56-46.94).[77] We found no research looking at NLR on day 3 between the sepsis and septic shock group. The trend we observed was probably because many sepsis patients recovered significantly on day 3, and their NLR value were close to normal, while many patients in septic shock required initiation of corticosteroid (27.4%).

Male patients had higher median NLR on day 1 (16.54, IQR: 8.45-26.78) and day 3 (16.69, IQR: 8.71-29.38). Female patients had a median NLR on day 1 of 13.15 (IQR: 9.03-20.50) and a median NLR on day 3 of 13.55 (IQR: 6.71-23.86). The differences of NLR on both day 1 and day 3 were not statistically different. Rehman et al also reported a similar value for NLR between males and females with sepsis (10.75 vs 9.70, p = 43).[98] In a study on reference value for NLR, the authors found a higher NLR in women less than 50 years old compared to men but lower NLR in women more than 50 years old. They suggested it due to the sex hormones as estrogen increases neutrophil recruitment. Pellegrino et al. also reported a higher number of neutrophils and NLR in females but not lymphocytes.[99] Sexual dimorphism in immune response has been studied extensively, and females tend to have more efficient, innate, and adaptive immune systems.[100] As a result, females are more susceptible to inflammatory and autoimmune diseases. However, the mean across all ages was 1.63±0.76 in men and 1.66±0.82 in women, which was quite similar.[39] A large sample of 9 427 patients in the United States was examined, and the mean NLR for male was 2.19 and for female was 2.11. No significant difference in NLR was observed between males and females.[38] Li et al. also reported that there was no significant difference in NLR between males and females in all age groups in healthy population.[101] In our result, the median between day 1 and day 3 for both sex were similar. We believed that there might be a possibility that sex altered NLR but this effect was minimal.

Our study's median NLR of 98 patients above 65 years old was 17.59 (IQR: 9.90-26.57). This was higher than the median of patients from 18 to 65, which was 13.96 (IQR: 6.73-21.75). This difference was not statistically significant. Li et al used one-way ANOVA to test the difference in NLR between different age groups and demonstrated that older age groups had higher NLR value compared to younger groups. With patients less than 20 years old, NLR was 1.53±0.56. Patients from 20-29, 30-39, 40-49, 50-59, 60-69, and above 70 had NLR of 1.62±0.50, 1.72±0.44, 1.77±0.40, 1.78±0.43, 1.83±0.52, and 1.99±0.60, respectively.[101] Pellegrino et al followed up on the InCHIANTI study's result and found a direct association between NLR and ages.[99] Aging causes the reduction in function of multiple organs and adaptive immunity can be tracked with thymus output which is represented by decreased lymphocytes.[102] Even though our result could not find a statistically differences in NLR between age groups, there was higher median for older population. We think that our population might not be large enough to show the difference as many researches have showed the effect of age on NLR.

❖ **Culture results, and treatment outcomes:**

On both day 1 and day 3, a higher median value of NLR was observed with patients with positive blood culture. The interquartile range was large. For example, on day 1, the IQR of patients with positive blood culture was 11.56 – 27.65 and the IQR of patients with negative blood culture was 8.45 – 23.61. There was no statistical difference when we grouped patients by blood culture results. We could not find research comparing NLR of patients with positive and negative blood culture in sepsis; however, as previously found that there was no association between blood culture positivity or negativity with in-hospital mortality, we did not expect NLR to be different. A larger sample will be needed to clarify this data.

We observed higher NLR median with patients with acute kidney injury compared to patients without acute kidney injury. However, we could only detect a statistical significance on day 3. Bu et al used multivariate logistic regression model and concluded that NLR was an independent predictor of septic AKI. A retrospective study with 222 adult patients in China found a median NLR of 20.43 (IQR: 11.61–36.23) for patients with AKI and a median NLR of 12.94 (IQR: 8.54–21.64). This difference was statistically significant. In this study, patients with AKI had both higher NLR and mortality.[86] Lower median but similar trend was found in another study published on Chest journal in 2020. This study also showed median NLR for patients with AKI (median: 14.14, IQR: 7.30-30.13) compared to patients without AKI (median:8.64, IQR: 3.76-16.8).[103] We believed that the correlation between NLR and AKI was due to their correlation with disease severity as we could not find a causal reason for kidney function to affect NLR. Patients who required CRRT had higher median NLR (median: 18.89, IQR: 11.03-33.76) compared to patents who did not require CRRT (median: 12.01, IQR: 8.44-21.49) on day 1 but this was not statistically significant. On the contrary, NLR on day 3 for patients who required CRRT (median: 22.67, IQR: 13.83-36.45) were higher than patients who did not required CRRT (median:13.54, IQR: 6.71-20.56). This was as expected because CRRT requirement was another indicator for kidney failure. A retrospective study published in 2022 in the relationship between NLR and AKI progression. Even though this study was not on sepsis, the authors found that NLR was an independent marker for AKI progression.[104]

In our study, the median NLR on day 1 for patients who required mechanical ventilation was lower than patients who did not require mechanical ventilation. However, we observed an opposite trend on day 3. None of these were statistically different. Most of the patients who required mechanical ventilation were among the pulmonary infection group (n = 48, percentage = 61.5%). A study in Egypt found a significantly higher rate of requirement for mechanical

ventilation in patients with NLR above 10 (59.4% vs 17.3%, p < 0.01). The cohort of this study was quite small (n=84) and their inclusion criteria was mostly on pulmonary infections.[48] We thought that the relationship that we found between mechanical ventilation requirement and mortality was because mechanical ventilation represented the severity of respiratory failure and the severity of the disease. We believed that our result could not detect any differences because respiratory failure only represented one organ and by itself, had small value on disease severity. When we divided the cohort using total bilirubin level to represent liver dysfunction, we also could not find any statistically significant difference between the two groups. However, we observed a higher median on both day 1 (19.12 vs 14.18) and on day 3 (20.29 vs 15.13) in patients with liver dysfunction which defined as total bilirubin level > 32 µmol/L. There were 31 patients with liver dysfunction (21.99%) while only six patients had total bilirubin above 100 µmol/L (4.26%). No patient in our study had fulminant liver failure. A large observational cohort study using data from seven states in the United States with 192 980 cases found that only 1.3% of patients had acute hepatic dysfunction. In this study, patients who had hepatic dysfunction had a mortality rate of 54.3%, which was much higher than the overall mortality of 28.6%.[105] We believed that with larger cohort, there might be a significant difference between these two groups.

4.2.2 Neutrophil to lymphocyte ratio and mortality

On day 1, the median NLR of the survivors was 12.02 (IQR: 8.25-20.38) and the non-survivors was 23.02 (IQR: 12.96-35.90). Using Mann-Whitney two-sample test, we identified a statistically significant difference between the two groups with a p value of less than 0.01. On day 3, the median NLR of survivors increased to 14.08 (IQR: 6.75-24.10) and the median NLR of non-survivors decreased to 20.93 (IQR: 14.76-37.92). However, survivors still had significantly higher NLR than non-survivors with a p value of less than 0.01. This difference was seen in many studies previously. A meta-analysis published on American Journal of Emergency Medicine in 2019 selected 14 studies with 11 564 patients to analyze the NLR. The authors reported a statistically higher NLR in non-survivors. In addition, higher NLR was associated with mortality and the hazard ratio was 1.75. These studies used different cut-offs for NLR, which ranged from 7 to 31. Heterogeneity was observed among the studies and it might decrease the robustness of the study. Most of the included studies were from Asian countries. The authors suggested this result needed to be validated in other regions.[3] A large study in Lebanon with 865 patients found a cut-off NLR value of 14.20 for in-hospital mortality. With this cut-off, the authors found that the area under the curve was 0.552 with sensitivity of 44.8% and specificity of 65.3%. Mortality of patients below the cut-off was 19.6%

while mortality of patients above the cut-off was 27.2%.[106] Rosa et al published a paper recently on Journal of Translational Medicine on NLR and hospitalized geriatric patients. 5 034 patients were included in the study with a mean age of 86.6±6.4. After using Cox regression analysis with four different models adjusting for different variables, the authors concluded that non-survivors had higher NLR compared to survivors. Sepsis and pneumonia were also reported as having highest NLR in this study.[49] Recently, a study from Spain found that the median NLR for survivors was 9.8 (IQR: 5.7-14.9) and the median NLR for non-survivors was 18.5 (IQR: 12.6-34.0). This result was statistically significant and more similar to ours.[46]

Salciccioli et al conducted a study with 5 056 critically ill patients to assess the relationship between NLR and mortality. They divided NLR into quantiles of less than 4.99, 4.99-8.90, 8.90-16.21, and more than 16.21. The mortality rate for each quantile from smallest to largest were 13%, 16%, 20%, and 28%. The differences were statistically significant. However, when the authors did a subgroup analysis, the correlation was strongest for non-sepsis patients and lost its' significance for sepsis patients.[44]

In general, our result largely agreed with many previous studies about NLR and sepsis mortality. NLR has been extensively validated in Asian population, especially Chinses. Our result showed that our population had many similarities with Chinese population. We believed that due to both the elevation of neutrophils in acute infection and the apoptosis of lymphocytes in hyperinflammatory state, neutrophil to lymphocyte ratio could reflect the severity of sepsis and became elevated in patients with poor outcome.

- **Correlation of neutrophil to lymphocyte ratio with SAPS II, mNUTRIC, and total bilirubin:**

From our study, we used logistic regression to identify values that correlate with NLR. Several values were acknowledged to have a correlation with NLR. Those are SAPS II score, mNUTRIC, and total bilirubin. Between NLR and SAPS II, we found a correlation coefficient of 0.09 ($p > 0.05$). This correlation was very weak and statistically insignificant. Similar results were also observed for mNUTRIC score and total bilirubin. mNUTRIC score has a correlation coefficient of 0.13 ($p > 0.05$) and total bilirubin has a correlation coefficient of 0.16 ($p > 0.05$) with NLR. Even though we could identify a few values that correlate with NLR, the correlation coefficients were small and statistically insignificant.

4.3 PREDICTIVE VALUE OF NEUTROPHIL TO LYMPHOCYTE RATIO

4.3.1 In-hospital predictive value models

- **Neutrophil to lymphocyte ratio and other severity scoring systems:**

We used receiver operating characteristic (ROC) curve analysis with Youden method to identify the area under the curve (AUC) and best cut-offs for NLR and four severity scoring systems including SOFA, APACHE II, SAP II, and mNUTRIC.

For NLR, the AUC was 0.68 with 95% CI from 0.60 to 0.76. Using Youden method, we found the best cut-off was 22.9 with a sensitivity of 51.1% and specificity of 81.25% for mortality. A study in Romania with 114 patients from October 2020 to June 2021 found an AUC of 0.631 (95% CI: 0.536-0.720) for a cut-off of 10.42. With this cut-off, the authors reported a sensitivity of 47% and a specificity of 78% for sepsis mortality.[48] Our result differed in cut-off value but was quite similar considering the AUC, sensitivity, and specificity. A study in Spain with 203 patients used ROC curve analysis for NLR on day 1, day 4, and day 8 to predict mortality. For day 1, day 4, and day 8, the AUC for NLR was 0.67 (95% CI: 0.60-0.73), 0.68 (95% CI: 0.61-0.75), and 0.75 (95% CI: 0.68-0.82). In this study, the cut-off for NLR in day 1 was 12.1.[46] A higher AUC of 0.77 (95% CI: 0.69-0.84) was reported for NLR in sepsis prognosis in China. The authors found the best cut-off was 8.25 with a high sensitivity of 95.8% and a low specificity of 48.1%.[50] Our results agreed with previous findings from multiple researches on the significant prognostic value of NLR in sepsis mortality. The cut-off that we found was on the higher end of the results from previous researches. However, the NLR value cut-off was flexible. A lower NLR value would increase sensitivity while a higher NLR value would increase specificity.

SOFA has been used as a primary assessment tool for sepsis as it is also a diagnosis criterion. SOFA has been extensively studied and validated in different populations. We found an AUC of 0.70 for SOFA score in in-hospital mortality and the best cut-off was 10 with a sensitivity of 66.7% and a specificity of 65.6%. A study in Turkey with 976 patients found an AUC of 0.72 for in-hospital mortality prediction. With a cut-off of 9, the sensitivity and specificity for in-hospital mortality was 65.8% and 75.5% respectively.[107] A retrospective cohort study published on JAMA including 182 Australian and New Zealand intensive care units with 184 875 patients also found an AUC of 0.753 (99% CI: 0.750-0.757) for in-hospital mortality.[108] For the Vietnamese population, a multicenter cross-sectional center with 252 patients found an AUC of 0.688 (95% CI: 0.618-0.715) for predicting in-hospital mortality and an AUC of 0.713 (95% CI: 0.643-0.783) for predicting ICU mortality. SOFA score of more than 8 was an independent factor for increased in-hospital mortality (OR: 2.717, 95% CI: 1.371-5.382), and SOFA score of more than 10 was an independent factor for ICU mortality (OR 2.194, 95% CI: 1.017-4.735).[68] We believe that the SOFA score is a valid prognostic tool for

Vietnam and other regions because multiple researchers found similar value of AUC and the best cut-off for SOFA score.

The mortality predictive value for APACHE II score was lower than SOFA in our result. The AUC was 0.65, and the best cut-off was 18, with a sensitivity of 82.2% and a specificity of 50.0%. Sadaka et al compared APACHE II and APACHE III in predicting sepsis mortality and found an AUC of 0.80 (95% CI: 0.78-0.82).[30] A study to validate APACHE II on sepsis mortality found an AUC of 0.639 (95% CI: 0.508-0.770).[109] In the Vietnamese population, the AUC of APACHE II was 0.689 (95% CI: 0.622-0.756) for in-hospital mortality and 0.672 (95% CI: 0.603-0.742) for ICU mortality.[68] Results of APACHE II in predicting in-hospital mortality were significant but varied among studies.

SAPS II score was found to have better AUC than SOFA score. SAPS II's AUC was 0.72 (95% CI: 0.64-0.79) and best cut-off was 39 with a sensitivity of 93.3% and a specificity of 42.7%. A study in Portugal found that the AUC for SAPS II in predicting in-hospital mortality was 0.662 (95% CI: 0.508-0.770).[109] ROC analysis of 203 patients admitted for sepsis in the ICU found an AUC of 0.738 for in-hospital mortality.[110] SAPS II was not commonly used for sepsis prognosis but several studies validated SAPS II for sepsis cohort and its value was comparable to SOFA score but those results were not consistent.[110]

In our study, mNUTRIC score had higher AUC value for in-hospital mortality compared to NLR and other severity scoring systems. With a cut-off of 5, the sensitivity and specificity of mNUTRIC score were 75.6% and 68.8% respectively. The AUC was 0.77 with a 95% confidence interval of 0.69-0.83. Welna et al reported an AUC of 0.83 (95% CI: 0.76-0.89) for mNUTRIC score for in-hospital mortality. The best cut-off in this study was 6 and the corresponding sensitivity and specificity were 90% and 64% respectively. A study in older population (80 and above) in Turkey also found an AUC of 0.841 (95% CI: 0.774-0.908) for mortality prediction. A cut-off of 5 in this study provide 95.9% sensitivity and 64.9% specificity.[111] mNUTRIC score was also tested in Vietnamese population and was found to have an AUC of 0.79 with 81% sensitivity and 67.1% specificity with a cut-off of 5.[112]

Overall, both NLR and four severity scoring systems provided significant AUC in hospital mortality. APACHE II had the lowest AUC and mNUTRIC had the highest AUC.

- **Neutrophil to lymphocyte ratio and some biological markers:**

Using ROC curve analysis, we found that age, lactate, and albumin also had significant AUC for in-hospital mortality prediction. Age had an AUC of 0.65 with 95% CI of 0.56-0.72.

A cut-off of 67 in age carried a 77.8% sensitivity and a 46.9% specificity. A study in 2019 found an AUC of 0.773 (95% CI: 0.661-0.884) for age in prediction hospital mortality. However, this study was conducted on 67 patients with intra-abdominal sepsis.[113] Using 6-hour lactate level, an AUC of 0.720 (95% CI: 0.670-0.765) was found for mortality prediction. Optimal cut-off was 3.5 mmol/L with a sensitivity of 60.8% and a specificity of 74.4%. However, in this study, they excluded patients with lactate of less than 2 mmol/L. It might better represent the more severe end of sepsis spectrum.[114] Chebl et al conducted a study with 939 septic patients to study the prognostic value of lactate and albumin. In this study, the AUC of lactate for hospital mortality was 0.60 (95% CI: 0.55-0.64).[115] A post-hoc analysis of INFAUCI study also found an AUC of 0.64 (95% CI: 0.61-0.72) for lactate in mortality prediction.[116]

As previously stated, many studies showed significant differences in age, lactate, and albumin between survivors and non-survivors, but we could not find studies calculating AUC of these values. In general, these values had lower AUCs than NLR and were not reliable.

- **Neutrophil to lymphocyte ratio combined with severity scoring systems:**

We tried to combine NLR and severity scoring systems to increase their value in predicting mortality in sepsis patients. When we combined NLR and SOFA score, we got an AUC of 0.75 with a 95% CI of 0.66-0.83. Combining NLR and APACHE II provided us with an AUC of 0.73 and a 95% CI of 0.64-0.81. Similarly, when we combined NLR and SAPS II, we got an AUC of 0.77 with a 95% CI of 0.69-0.85. Our best value was when we combined NLR with mNUTRIC score, which provided an AUC of 0.81 and a 95% CI of 0.73-0.89.

Li et al conducted a study to evaluate the combination of NLR and SOFA in sepsis prognosis. In this study, SOFA score alone had an AUC of 0.791 and NLR alone had an AUC of 0.721. When the authors combined NLR and SOFA score, AUC was improved to 0.868 with a 95% CI of 0.824-0.911.[117] We could not find other studies evaluating the AUC of combining NLR with other severity scoring systems. However, combining NLR to other severity scoring systems could improve their prognostic value for hospital mortality.

- **Comparison of the predictive values of neutrophil to lymphocyte ratio and other markers:**

We used DeLong's test to compare the performance of our previously chosen prognostic models. We compared the NLR model with SOFA, APACHE II, SAPS II, mNUTRIC, lactate, and albumin.

Of all the models, SOFA, SAPS II, and mNUTRIC had higher AUC than NLR. APACHE II, lactate, and albumin had lower AUC than NLR. However, we could not find a statistically significant difference between NLR and any prognostic model.

4.3.2 Univariate analysis of neutrophil to lymphocyte ratio and other markers for mortality

We performed a univariate analysis for NLR and other markers for mortality. Maizel et al. also performed a univariate analysis on sepsis mortality and found that age, baseline GFR and SAPS II were statistically significant. In this study, hazard ratios for age, baseline GFR, and SAPS II were 1.02, 0.99, and 1.04, respectively. They did not observed a significant different with male sex.[118] The effect of age and SAPS II score to mortality was lower than us (1.04 vs 1.02 and 1.06 vs 1.04, respectively). A study in China with 72 patients found a OR for APACHE II, SOFA, and lactate were 1.449 (95% CI: 1.208-1.738), 1.974 (95% CI: 1.433-2.719), and 2.873 (95% CI: 1.616-5.108), respectively.[119] Another study in China with 333 patients reported that APACHE II score, NLR, and age were risk factors for mortality in their univariate analysis. The ORs for APACHE II score, NLR, and age were 1.168 (95% CI: 1.102-1.238), 1.038 (95% CI: 1.008-1.070), and 1.085 (95% CI: 1.039-1.132), respectively.[120]

Liao et al conducted a study with 127 patients with sepsis and used univariate analysis to identify 28-day mortality risk factors. WBC, CRP, PCT, SOFA, and NLR of more than 8.25 were risk factors for 28-day mortality. The OR for SOFA in this study was the same as ours at 1.24. The OR for NLR more than 8.25 was 6.39.[50] A retrospective observational study published in 2021 on the prognostic value of NLR and interleukin-6 found an OR of 1.340 (95% CI: 1.253-1.434) for NLR (cut-off 4.937).[121] We believed that there were enough evidence to support our result that NLR was a risk factor for mortality.

4.3.3 Multivariate analysis of a predictive model for sepsis mortality

From our univariate analysis, we chose age, male sex, AKI, mechanical ventilation, number of comorbidities, SOFA, NLR, and lactate in our multivariate logistic regression analysis. We decided to omit CRRT as it was a similar indicator for acute kidney injury. APACHE II, SAPS II, and mNUTRIC were omitted because they were also severity scoring systems, but all were not validated, as well as SOFA in sepsis patients. Our result showed that age, male sex, AKI, number of comorbidities, SOFA, and lactate lost their significance in our model. However, NLR was an independent risk factor for sepsis mortality. With every point increase in NLR, the patient's mortality rate increases by 3%. The need for mechanical ventilation was also found to be an independent risk factor with an OR of 4.28.

A study with 146 patients with sepsis in China used multiple regression analysis and found that NLR was an independent risk factor for death at 28 days with an OR of 1.669 (95% CI: 1.402-1.987).[122] Lorente et al also reported an association between NLR and 30-day mortality on day 1, day 4, and day 8 in their multiple logistic regression analysis. They found the ORs for day 1, day 4, and day 8 were 1.049 (95% CI: 1.022-1.-76), 1.026 (95% CI: 1.008-1.045), and 1.044 (95% CI: 1.009-1.079).[46] Liu et al. reported that the APACHE II score, NLR, and age were independent predictors of mortality in their multivariate logistic regression analysis. In this study, the OR of NLR was 1.043 (95% CI: 1.012-1.083) which was similar to our result. However, age lost its' significant in our multivariate analysis.[120] Liu et al reported a OR of 1.283 (95% CI: 1.167-1.410) and 1.281 (95% CI: 1.159-1.414) for NLR (cut-off: 4.937) in their two multivariate sepsis prognostic models.[121]

All in all, as we found that the prognostic value of NLR in mortality prediction in patients with sepsis was maintained in many multivariate logistic regression analyses in different studies, we believed that the NLR was an excellent mortality prediction tool in sepsis.

4.4 STUDY LIMITATIONS

This was a single-center, retrospective study with 141 patients included. The sample size was small, and the population of the study was confined to Northern regions of Vietnam, which made the study prone to selection bias.

In addition, because the study excluded patients with hematological disorders and malignancy, the results cannot be applied to that population.

CONCLUSION

In our single-center retrospective observational study involving 141 patients with sepsis or septic shock, our findings can be summarized as follows:

1. **Neutrophil to lymphocyte ratio changes in patients with sepsis or septic shock:**

- NLR on day 3 in septic shock patients was higher than in sepsis patients.
- NLR on day 3 in patients who had AKI was higher than patients who did not have AKI.
- NLR on day 3 in patients who required continuous renal replacement therapy (CRRT) was higher than patients who did not.
- Non-surviving patients had higher NLRs on both day 1 and day 3 compared to surviving patients.
- No significant difference in NLR on day 1 was observed when patients were grouped by acute kidney injury and CRRT requirement.
- There was no significant difference in NLR on both day 1 and day 3 between patients grouped by sex (male, female), age group (18-65, >65), blood culture result (positive, negative), mechanical ventilation requirement, and liver dysfunction.

2. **The correlation of Neutrophil to lymphocyte ratio with some prognostic factors of severity and mortality in patients with sepsis and septic shock**

- Weak correlations were found between NLR and SAPS II score, mNUTRIC score, and bilirubin levels, but these correlations were not statistically significant.
- NLR had predictive value for in-hospital mortality in patients with sepsis and septic shock. In ROC curve analysis, the AUC of NLR was 0.68 with a 95% CI of 0.60 – 0.76. The best but-off value was 22.9 with 51.1% sensitivity and 81.25% specificity.
- NLR exhibited similar predictive value for in-hospital mortality to SOFA, APACHE II, SAPS II, mNUTRIC, age, serum lactate level, and albumin level.
- NLR had a similar in-hospital predictive value to age, lactate, and albumin.
- When integrated with severity scoring systems, NLR enhanced the AUCs of SOFA, APACHE II, SAPS II, and mNUTRIC to 0.75, 0.73, 0.77, and 0.81, respectively.
- NLR was identified as an independent predictor of in-hospital mortality in patients with sepsis and septic shock.

RECOMMENDATION

Neutrophil to lymphocyte ratio should be applied into clinical practice in treating patients with sepsis or septic shock because it is available in almost all healthcare facilities, is very cheap to obtain, and carries good prognostic value by itself or combining with other severity scoring systems.

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THE LIST OF PATIENTS IN THE STUDY

Number	Name	Sex	Age	Admission	Hospital ID
1	Đặng Quốc K.	Male	64	01/04/2021	21902960
2	Trần Thị Mỹ V.	Female	20	01/06/2021	21933967
3	Nguyễn Thế T.	Male	75	01/10/2021	21949237
4	Đỗ Văn T.	Male	75	02/03/2021	22104197
5	Trần Thị T.	Female	75	02/03/2021	21876831
6	Đỗ Ngọc Q.	Male	87	02/04/2021	21957486
7	Đỗ Văn T.	Male	71	02/04/2021	21488809
8	Phạm Xuân P.	Male	92	02/10/2021	21959434
9	Hồ Viết Đ.	Male	63	02/12/2021	22027313
10	Lê Đình T.	Male	50	02/12/2021	21575846
11	Nguyễn Văn H.	Male	44	03/11/2021	22163297
12	Nguyễn Văn T.	Male	77	03/12/2021	21624409
13	Dương Bá B.	Male	71	04/02/2021	21972887
14	Trần Thị H.	Female	64	04/03/2021	21387310
15	Nguyễn Huy P.	Male	62	04/03/2021	22167446
16	Đỗ Đăng Kh.	Male	49	04/04/2021	21576576
17	Trần Văn Nh.	Male	79	04/06/2021	21456742
18	Đỗ Thị K.	Female	91	05/01/2021	21560009
19	Phạm Quang S.	Male	67	05/03/2021	21581545
20	Bế Hồng C.	Male	66	05/08/2021	21520202
21	Nguyễn Thị N.	Female	57	05/09/2021	21952116
22	Lê Thị H.	Female	70	05/10/2021	22122986
23	Phạm Đ.	Male	93	05/11/2021	22038964
24	Chu Văn H.	Male	82	05/11/2021	21444053
25	Hoàng Thị D.	Female	82	06/03/2021	21921793

26	Vũ Văn C.	Male	79	06/07/2021	21542050
27	Trần Xuân Q.	Male	99	06/12/2021	22110257
28	Lại Thị T.	Female	71	07/06/2021	22104090
29	Bùi Thị S.	Female	72	08/06/2021	21711554
30	Trần Doãn T.	Male	92	08/11/2021	21479489
31	Trần Thị O.	Female	70	08/12/2021	21962141
32	Vũ Đình M.	Male	48	09/04/2021	21408358
33	Lê Tuấn Kh.	Male	76	09/09/2021	21368702
34	Lê Thị H.	Female	87	10/03/2021	21667859
35	Nguyễn Văn T.	Male	68	10/03/2021	22086004
36	Hoàng Công T.	Male	57	10/06/2021	21911128
37	Nguyễn Thị N.	Female	73	11/07/2021	21418046
38	Phan Thị T.	Female	48	11/11/2021	21923514
39	Mai Thị Ch.	Female	81	12/11/2021	21483741
40	Phùng Thị L.	Female	67	13/01/2021	22051413
41	Nguyễn Thị Đ.	Female	73	13/05/2021	22027702
42	Đỗ Ngọc H.	Male	67	13/10/2021	21939185
43	Tưởng Phi Đ.	Male	91	13/10/2021	21967584
44	Phạm Văn Đ.	Male	75	14/09/2021	21365285
45	Từ Minh T.	Male	70	14/10/2021	21747777
46	Nguyễn Lê T.	Male	75	14/10/2021	21480002
47	Hoàng Đ.	Male	77	15/01/2021	21876247
48	Bùi Đặng T.	Male	63	15/06/2021	21765808
49	Trịnh Ngọc C.	Male	55	17/01/2021	21987635
50	Phạm Thị H.	Female	71	18/03/2021	21893835
51	Đỗ Như C.	Male	80	18/10/2021	21576223
52	Nguyễn Thị B.	Female	77	18/11/2021	22038569
53	Lục Minh H.	Male	62	19/01/2021	21655020

54	Đoàn Đình H.	Male	67	19/10/2021	21534150
55	Nguyễn Thiện T.	Male	77	20/02/2021	21867438
56	Nguyễn Hoa T.	Male	81	20/08/2021	22086184
57	Trần Đình N.	Male	91	20/08/2021	21926089
58	Vũ Thị N.	Female	86	21/01/2021	22049198
59	Nguyễn Phú D.	Male	58	21/11/2021	21937113
60	Đỗ Như S.	Male	79	22/05/2021	21568620
61	Tạ Quang H.	Male	92	22/07/2021	22113924
62	Trịnh Cao Th.	Male	78	23/01/2021	21799180
63	Nguyễn Bá S.	Male	70	23/10/2021	22063870
64	Trần Nam T.	Male	66	23/12/2021	21558859
65	Nguyễn Thị N.	Female	80	24/08/2021	21324423
66	Phạm Quang T.	Male	62	25/06/2021	21976281
67	Phạm Bá X.	Male	76	25/09/2021	22049204
68	Lê Đức T.	Male	91	27/02/2021	21858847
69	Nguyễn Tiến K.	Male	61	30/05/2021	21934450
70	Nguyễn Thị T.	Female	81	24/11/2021	22096649
71	Nguyễn Vĩnh L.	Male	79	14/12/2021	22141783
72	Trần Huy Q.	Male	94	17/12/2021	22155075
73	Nguyễn Văn Q.	Male	54	26/12/2021	22171082
74	Phạm Thị N.	Female	84	27/12/2021	22173179
75	Trần Văn H.	Male	67	30/12/2021	22182815
76	Nguyễn Duy C.	Male	60	03/01/2022	22189030
77	Trần Huy Q.	Male	95	11/01/2022	22207228
78	Phạm Đ.	Male	95	27/01/2022	22243535
79	Phạm Thị T.	Female	76	28/01/2022	22245702
80	Trần Lê N.	Male	93	01/02/2022	22246397
81	Tưởng Duy H.	Male	93	04/02/2022	22246802

82	Mai Anh T.	Female	79	04/02/2022	22246887
83	Hà Thị N.	Female	86	07/02/2022	22249788
84	Nguyễn Ngọc H.	Male	67	09/02/2022	22255802
85	Lương Xuân D.	Male	62	10/02/2022	22255965
86	Lê N.	Male	90	10/02/2022	22257662
87	Vũ Hưng B.	Male	58	15/02/2022	22265420
88	Nguyễn Đức C.	Male	53	21/02/2022	22280475
89	Mai Văn Đ.	Male	74	22/02/2022	22282663
90	Dương Tấn N.	Male	93	23/02/2022	22283912
91	Nguyễn Duy T.	Male	82	02/03/2022	22295936
92	Nguyễn Thị H.	Female	40	05/03/2022	22299753
93	Nguyễn Thị T.	Female	81	08/03/2022	22305566
94	Nguyễn Thị C.	Female	68	13/03/2022	22313979
95	Vũ Ngọc P.	Male	75	15/03/2022	22318665
96	Nguyễn Thị P.	Female	85	20/03/2022	22332142
97	Triệu Quốc H.	Male	57	22/03/2022	22340016
98	Đào Thị L.	Female	84	24/03/2022	22347591
99	Hà Thị N.	Female	62	03/04/2022	22372756
100	Nguyễn Quốc T.	Male	86	05/04/2022	22376944
101	Phạm Thị D.	Female	78	05/04/2022	22380242
102	Lê Đắc A.	Male	58	15/04/2022	22412469
103	Nguyễn Văn S.	Male	65	21/06/2022	22640350
104	Nguyễn Văn Q.	Male	66	21/06/2022	22636362
105	Đặng Thị H.	Male	65	15/06/2022	22613437
106	Hà Hữu K.	Female	67	13/06/2022	22606980
107	Lê Thị Đ.	Female	80	04/06/2022	22573171
108	Vũ Đăng T.	Male	76	01/05/2022	22459626
109	Trần Thị Thanh T.	Female	91	02/06/2022	22568978

110	Trần Bá N.	Male	55	23/05/2022	22526522
111	Nguyễn Văn V.	Male	84	10/05/2022	22485200
112	Nguyễn Mạnh C.	Male	64	25/06/2022	22656331
113	Bùi Văn C.	Male	81	12/07/2022	22715602
114	Nguyễn Đức Q.	Male	63	12/07/2022	22718302
115	Đinh Văn T.	Male	75	16/07/2022	22734874
116	Trần Quang V.	Male	51	29/07/2022	22787539
117	Nguyễn Văn B.	Male	56	01/08/2022	22789033
118	Vũ Thị Đoàn T.	Female	77	03/08/2022	22803890
119	Bùi Thị K.	Female	78	05/08/2022	22813275
120	Hồ Thị T.	Female	76	06/08/2022	22813312
121	Bùi Thế H.	Male	70	08/08/2022	22819344
122	Bùi Thế T.	Male	65	17/08/2022	22855664
123	Diêm Trọng S.	Male	59	18/08/2022	22859410
124	Nguyễn Khắc Q.	Male	65	21/08/2022	22867189
125	Thái U.	Male	93	26/08/2022	22889655
126	Nguyễn Văn C.	Male	68	06/09/2022	22918242
127	Nguyễn Ngọc S.	Male	77	07/09/2022	22923500
128	Nguyễn Trọng B.	Male	24	16/09/2022	22953966
129	Mai Quý V.	Male	64	05/10/2022	23023202
130	Bùi Quang Đ.	Male	65	13/10/2022	23059630
131	Nguyễn Xuân H.	Male	66	28/10/2022	23108253
132	Lương Anh T.	Male	70	08/11/2022	23145409
133	Đỗ Đình N.	Male	48	12/11/2022	23164105
134	Nguyễn Thị D.	Female	66	21/11/2022	23195044
135	Nguyễn Tiến P.	Male	50	24/11/2022	23208683
136	Ngô Thị T.	Female	88	28/11/2022	23219715
137	Nguyễn Văn T.	Male	54	29/11/2022	23224300

138	Trần Thanh T.	Male	100	30/11/2022	23228173
139	Phạm Thị T.	Female	70	30/11/2022	23228868
140	Nguyễn Ngọc B.	Male	66	07/12/2022	23251763
141	Nguyễn Văn H.	Male	90	08/12/2022	23255857

Hanoi, January 14, 2024

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Degree: Bác sĩ nội trú	
Advisor(s): Dr. Pham Dang Hai	
Title of the study: The prognostic value of neutrophil to lymphocyte ratio in patients with sepsis and septic shock in medical intensive care unit of 108 Central Military Hospital	
Document type: Thesis	
Please supply 5 keywords for the study (Use subject heading from https://authorities.loc.gov/):	**1.** Sepsis **2.** Neutrophil to lymphocyte ratio **3.** Prognostic value **4.** 108 Central Military Hospital **5.** Mortality

Abstract/Summary

- **BACKGROUND:**

Sepsis is a serious condition with high mortality. Prompt stratification and treatment are required to decrease its' morbidity and mortality. Neutrophil to lymphocyte ratio (NLR) has been found to have reasonable prognostic value for sepsis mortality. This study aims to evaluate NLR as a prognostic tool for in-hospital mortality in patients with sepsis and septic shock.

- **METHOD:**

The study was designed as a single-center retrospective cohort in the Medical Intensive Care Unit of 108 Central Military Hospital from January 2021 to December 2022. A total of 141 cases of newly diagnosed sepsis or septic shock were included. In-hospital mortality was the primary outcome.

- **RESULTS:**

The overall mortality was 31.9%. NLR on day 3 was significantly higher in patients with septic shock diagnosis, patients with AKI, and patients who required CRRT. NLR was significantly higher in non-survivors on both day 1 and day 3. NLR had an AUC of 0.68 with a 95% CI of 0.60 – 0.76 in predicting in-hospital mortality. NLR has similar predictive value in predicting in-hospital mortality with SOFA, APACHE II, SAPS II, and mNUTRIC. The best cut-off for NLR was 22.9 with a sensitivity of 51.1% and a specificity of 81.25%. Higher NLR was independent predictors for in-hospital mortality.

- **CONCLUSION:**

NLR was an independent predictor of in-hospital mortality and had significant predictive value for poor outcomes in patients with sepsis.

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