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PROGNOSTIC VALUE OF NEUTROPHIL - LYMPHOCYTE RATIO IN PREDICTING MORTALITY IN PATIENTS WITH SEPSIS AND SEPTIC SHOCK

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ABSTRACT

BACKGROUND: A multitude of required and non-necessary changes are linked to infections, and in extreme situations, these changes necessitate prompt attention as infections can be life-threatening and cause serious organ malfunction, which can lead to organ failure and death. Sepsis is a very common and complicated condition and is faced by both the developing and developed world. The global epidemiological burden of sepsis is difficult to ascertain. It is estimated to affect more than 30 million people worldwide every year, potentially leading to 6 million deaths.

MATERIALS AND METHODS: A hospital based prospective study was conducted patients admitting in MICU and RICU at Basaveshwara Medical College Hospital, Chitradurga during the study period of 18 months from August 2022 to February 2024. Clearance from institution ethics committee was taken before the study was started. An informed consent was taken before including the study subjects in to the study.

RESULTS: There was no statistically significant difference in cases with neutrophil lymphocyte ratio of less and more than 3. There was a statistically significant difference in the neutrophil count in cases with neutrophil lymphocyte ratio of less than 3 and more than 3.

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There was no statistically significant difference between the cases with neutrophil lymphocyte ratio of less and more than 3 with respect to lymphocyte counts at admission.

CONCLUSION: This study was undertaken in order to study neutrophil lymphocyte ratio as a prognostic marker in cases of severe sepsis. This study had shown that, NLR was shown to be an important and readily available marker prognosis of sepsis. But this study is not without limitations. This used a convenience sample method where study results cannot be generalized.

KEYWORDS: Neutrophil, Lymphocyte, Mortality, Shock.

INTRODUCTION

A multitude of required and non-necessary changes are linked to infections, and in extreme situations, these changes necessitate prompt attention as infections can be life-threatening and cause serious organ malfunction, which can lead to organ failure and death. Sepsis is a very common and complicated condition and is faced by both the developing and developed world. The global epidemiological burden of sepsis is difficult to ascertain. It is estimated to affect more than 30 million people worldwide every year, potentially leading to 6 million deaths.[1] Sepsis is linked to a series of organ failures as well as system failures; therefore, intervention is necessary to control and stop the damage from getting worse while also making sure the patient receives the right care to recover.[2] According to evidence from the literature that is currently accessible, sepsis is a public health concern that affects patients of all ages and is associated with greater rates of morbidity and death in those who require severe ICU hospitalisation.[3] As per sepsis 3 definition, Sepsis is a lie threatening organ dysfunction caused by a dysregulated patient response to infection. Sepsis is a condition and is associated with high incidence of mortality if not recognised and appropriate measures are initiated. The new definition also implied that sepsis should be triggered by an underlying infection. Septic

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shock is defined as a subset of sepsis which is characterised by profound hypotension. The new definition doesn't focus on inflammation as a criteria, but focuses on hypo perfusion and organ dysfunction.[4] The incidence rate of severe sepsis in patients was found to be 16.45% in India. Additionally, it is anticipated that the global incidence of sepsis would rise at a rate of 1.5% annually, which is concerning and calls for appropriate preventive measures.[5] The important principle for the appropriate management of sepsis is early and accurate detection of the patients at high risk for complications and death. The traditional approach to the diagnosis of sepsis is based on the clinical findings and the symptoms and also supported by microbiological data.

In response to infection, sepsis is known to set off a series of reactions that include the production of inflammatory mediators as a defence against microorganisms and their harmful byproducts. However, because they cause cellular damage, which can result in organ malfunction and changes in the serum level of components, these inflammatory mediators have both a protective and a destructive effect. These are more widely known as "biomarkers" and may serve as an indicator of the extent of damage. They can also be an effective assessment tool.[6] One of the main setbacks in the management of sepsis is to ascertain the prognosis. Various markers have been studied for ascertaining the prognosis such white blood cells, C reactive protein and pro calcitonin. These have been used in predicting the prognosis, but each of these tests have some limitations. For example, Pro calcitonin, even though it is valuable in predicting the prognosis, cost factor is a great limitation. Thus, there requires the need to find a cost effective and reliable marker for prognosticating patient who are admitted with sepsis. Zahorec et al. were the first to propose to use the ratio of neutrophil and lymphocyte count (NLCR) as an additional infection marker in clinical practice.[7]

Neutrophil to lymphocyte ratio (NLR) is calculated by dividing the neutrophil count and the lymphocyte count which are calculated from the white cell differential blood count

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from the patient at the time of admission. Increased Neutrophil Lymphocyte values were found to be associated with unfavourable clinical prognosis in patients with sepsis.[8] One of the physiological responses in the immune system against systemic inflammation is an increase in the number of neutrophils and the decrease in the number of lymphocytes and this is the rationale behind selecting neutrophil lymphocyte ratio. This is due to changes in the dynamics and regulation of apoptosis in a state of systemic inflammation when compared with non-inflammatory state.[9] A study published in the Asian journal of Medical Sciences, published in the year 2018, shows that an increased neutrophil Lymphocyte ratio was associated with poor outcome in patients admitted with sepsis.[10] But there is paucity of the literature in this part of the country in order to study the utilization of Neutrophil – lymphocyte ration in predicting mortality of the patients with sepsis or septic shock. This study aims to find an association with neutrophil lymphocyte ratio as a prognostic marker in patients with sepsis and septic shock.

MATERIAL AND METHODS

A hospital based prospective study was conducted patients admitting in MICU and RICU at Basaveshwara Medical College Hospital, Chitradurga during the study period of 18 months from August 2022 to February 2024. Clearance from institution ethics committee was taken before the study was started. An informed consent was taken before including the study subjects in to the study. A total of 30 cases constituted the study sample. The inclusion and exclusion criteria were as follows,

Inclusion criteria

- Age > 18 years
- Sepsis, due to any cause.
- Blood sampling within 24 hours after ICU admission
- Blood samples to be taken before the initiation of antibiotics.

Exclusion criteria:

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- Patients who have had prior administration of antibiotics before blood sampling (up to one week before admission).
- Patients with immunosuppressive diseases like HIV, cancer.
- Patients on immunosuppressive therapy
- Patients who were admitted in the ICU and developed nosocomial infection leading to secondary sepsis.

Statistical analysis

The collected was entered in an excel sheet and transferred and analysed using SPSS (ver 20). The categorical variables were presented as frequencies and percentages. Chi square test was used as test of significance. Quantitative variables were presented as Mean and Standard deviation. An independent sample T test was applied as test of significance. Receiver Operating Characteristic was conducted to decide the predictive accuracy. A p value of less than 0.05 was considered as statistically significant.

RESULTS

Table 1. Distribution of the study group according to Neutrophil count

Neutrophil (Mean ± SD)	Neutrophil Lymphocyte Ratio		T value	P value, Sig
	< 3	> 3		
Admission	66.6 ± 8.1	66.3 ± 5.3	0.201	0.841, NS

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24 hours	59.4 ± 7.2	78.8 ± 6.7	16.860	0.000, Sig
72 hours	66.6 ± 8.1	66.3 ± 5.3	8.781	0.000, Sig

There was no statistically significant difference in cases with neutrophil lymphocyte ratio of less and more than 3. There was a statistically significant difference in the neutrophil count in cases with neutrophil lymphocyte ratio of less than 3 and more than 3.

Table 2. Distribution of the study group according to Lymphocyte count

Lymphocyte (Mean ± SD)	**Neutrophil Lymphocyte Ratio**		**T value**	**P value, Sig**
	< 3	**> 3**		
Admission	22.3 ± 7.2	22.8 ± 6.7	0.431	0.667, NS
24 hours	37.3 ± 6.2	17.7 ± 4.4	21.204	0.000, Sig
72 hours	34.4 ± 3.4	28.7 ± 6.3	7.652	0.000, Sig

There was no statistically significant difference between the cases with neutrophil lymphocyte ratio of less and more than 3 with respect to lymphocyte counts at admission. There was a statistically significant difference between cases with neutrophil lymphocyte ratio of less and more than 3 at 24 hours and 72 hours.

Table 3. Distribution of the study group according to total count

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TC (Mean ± SD)	Neutrophil Lymphocyte Ratio		T value	P value, Sig
	< 3	> 3		
Admission	8569.4 ± 2755.6	10138.4 ± 25975	3.555	0.000, Sig
24 hours	7299.7 ± 1841.9	10833.4 ± 1317.6	12.826	0.000, Sig
72 hours	6754.0 ± 2089.5	7687.1 ± 1327.0	3.051	0.003, Sig

There was a statistically significant difference in total count between the cases with neutrophil lymphocyte ratio of less than and more than 3 at admission, 24 hours and 72 hours.

Table 4. Distribution of the study group according to Neutrophil lymphocyte ratio at 24 hours

NLR (Mean ± SD)	Neutrophil Lymphocyte Ratio		T value	P value, Sig
	< 3	> 3		
24 hours	1.66 ± 0.48	5.0 ± 2.6	13.121	0.000, Sig

Mean neutrophil lymphocyte ratio at 24 hours was 1.66 in cases with neutrophil lymphocyte ratio of less than 3 and 5.0 in cases with neutrophil lymphocyte ratio of more than 3. This difference was statistically significant.

Table 5. Distribution of the study group according to ICU admission

ICU admission	Neutrophil Lymphocyte Ratio

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	< 3 n (%)	> 3 n (%)
Yes	114 (100)	56 (100)
Total	114 (100)	56 (100)

Table 6. Distribution of the study group according to Outcome

Death	**Neutrophil Lymphocyte Ratio**	
	< 3 **n (%)**	**> 3** **n (%)**
No	100 (87.7)	49 (87.5)
Yes	14 (12.3)	7 (12.5)
Total	114 (100)	56 (100)

χ^2 value=0.002 df=1 p value, Sig=0.967, NS

About 12.3% cases with neutrophil lymphocyte ratio of less than 3 and 12.5% of the cases with neutrophil lymphocyte ratio of more than 3. This difference was not statistically significant.

DICSUSSION

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Infections are associated with a wide range of necessary and unnecessary alterations, some of which require immediate intervention in severe cases because infections can be fatal or seriously compromise organ function. Sepsis is a highly prevalent and intricate illness that affects people in both developed and underdeveloped nations. It is challenging to determine the epidemiological burden of sepsis worldwide. It is thought to impact about 30 million individuals globally year and may result in 6 million fatalities.[1] Because sepsis is associated with a number of organ and system failures, intervention is required to manage the condition, prevent further damage, and ensure the patient gets the treatment they need to recover.[2] Sepsis is a public health hazard that affects patients of all ages and is linked to higher rates of morbidity and death in those who require severe ICU hospitalization, according to evidence from the literature that is currently accessible.[3] Sepsis, according to the definition given in Sepsis 3, is a life-threatening organ malfunction brought on by a patient's dysregulated response to an infection. Sepsis is a medical illness that carries a significant death rate if it is not identified and treated appropriately. Additionally, the revised definition suggested that an underlying infection should be the cause of sepsis. A subgroup of sepsis known as "septic shock" is characterized by severe hypotension. The new definition places more emphasis on organ dysfunction and hypoperfusion than it does on inflammation as a criterion.[4] In India, it was discovered that the incidence rate of severe sepsis in patients was 16.45%. Furthermore, a 1.5% annual increase in the global incidence of sepsis is predicted, which is alarming and necessitates the implementation of suitable preventive measures.[5] Identifying patients who are at high risk of complications and mortality early on is crucial for the proper management of sepsis. The conventional method of diagnosing sepsis is based on the symptoms and clinical findings, with additional support from microbiological evidence. Sepsis is known to initiate a cascade of events in response to infection, one of which is the generation of inflammatory mediators as a defense mechanism against bacteria and their pathogenic consequences. However, these

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inflammatory mediators have both a protective and a destructive effect since they produce cellular damage, which can lead to organ malfunction and changes in the serum level of components. These are more commonly referred to as "biomarkers" and could be used to gauge the degree of damage. They may also be a useful instrument for assessments.[6] Determining the prognosis is a major obstacle in the therapy of sepsis. Numerous indicators, including procalcitonin, C reactive protein, and white blood cells, have been investigated to determine prognosis. Although there have been some limits to each of these tests, they have all been utilized to determine prognoses. For instance, the cost factor is a significant barrier for procalcitonin, notwithstanding its value in prognostic prediction. Finding an accurate and affordable marker to predict the prognosis of patients who are admitted with sepsis is therefore necessary. The ratio of neutrophil to lymphocyte count (NLCR) was initially proposed for use as an extra infection marker in clinical practice by Zahorec et al.[7]

The neutrophil to lymphocyte ratio (NLR) is computed by dividing the counts of neutrophils and lymphocytes, which are derived from the patient's entrance white cell differential blood count. Higher levels of neutrophil lymphocytes have been linked to a worse clinical outcome for sepsis patients.[8] The neutrophil lymphocyte ratio was chosen because it represents one of the immune system's physiological responses to systemic inflammation, which is an increase in neutrophils and a decrease in lymphocytes. This is because, in contrast to a non-inflammatory condition, the kinetics and regulation of apoptosis differ in a state of systemic inflammation.[9] According to a 2018 study that appeared in the Asian Journal of Medical Sciences, individuals who were admitted with sepsis had worse outcomes when their neutrophil to lymphocyte ratio was higher.[10] However, there is a dearth of research on the use of neutrophil-lymphocyte ratio in predicting patient death in sepsis or septic shock in this region of the nation. The purpose of this research is to determine whether the neutrophil

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lymphocyte ratio is associated with prognosis in individuals suffering from sepsis and septic shock.

SOFA scores

Between 24 and 48–72 hours, there was no statistically significant difference in SOFA values. In a study by Zhang et al, the mean SOFA score was 3 in survivors and 3 in non survivors.[13] In a study by Shi et al, the median SOFA was 8 in survivors and 9 in non survivors.[11]

Neutrophil count

In cases where the neutrophil lymphocyte ratio was less than or greater than three, there was no statistically significant difference. The neutrophil count varied statistically significantly between cases where the neutrophil lymphocyte ratio was less than three and more than three. In a study by Qiu et al, the mean neutrophil count was 8.25×10^9/L.[12] IN a study by Shi et al, the median neutrophil count was 7.23×10^9/L in survivors and 10.11×10^9/L in non survivors.[11]

Lymphocytes

Regarding the lymphocyte counts upon admission, there was no statistically significant difference between the cases with a neutrophil lymphocyte ratio of less than three and those with a ratio of more than three. In a study by Qiu et al, the lymphocyte count was 0.46×10^9/L.[12] In a study by Shi et al, the mean lymphocyte count was 0.91×10^9/L in survivors and 0.74 in non survivors.[11]

Total count

Between the cases with neutrophil lymphocyte ratios of less than and more than 3 at admission, 24 hours, and 72 hours, there was a statistically significant difference in the total count. In a study by Qiu et al, the total count was 9.33×10^9/L.[12]

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NLR after 24 hours

In situations where the neutrophil lymphocyte ratio was less than three, the mean neutrophil lymphocyte ratio at 24 hours was 1.66; in cases where the neutrophil lymphocyte ratio was greater than three, it was 5.0. There was a statistically significant difference. In a study by Qiu et al, the neutrophil lymphocyte ratio was 16.08 in survivors and 39.64 in non survivors.[12] In a study by Zhang et al, the mean NLR was 10.56 in survivors and 17.04 in non survivors. In a regression analysis the 28 day mortality was significantly associated with NLR.[13] In a study by Shi et al, the median NLR was 9.91 in survivors and 11.23 in non survivors.[11]

ICU stay

Every case in both groups was brought to the Intensive Care Unit for treatment. In a study by Shi et al, the mean duration of ICU stay was 5 days in survivors and 7 days in non survivors.[11]

Outcome In 12.3% of instances, the neutrophil lymphocyte ratio was less than three, while in 12.5% of cases, it was greater than three. There was no statistically significant difference. In a study by Qiu et al, the total mortality was 53.49%.[12]

CONCLUSION

This study was undertaken in order to study neutrophil lymphocyte ratio as a prognostic marker in cases of severe sepsis. This study had shown that, NLR was shown to be an important and readily available marker prognosis of sepsis. But this study is not without limitations. This used a convenience sample method where study results cannot be generalized. A study with elegant methodology can bring out more facts about usefulness of Neutrophil lymphocyte as a marker in prognosis of sepsis patients. But this study had brought

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out important facts about usefulness of neutrophil lymphocyte ration in prognosis. Further studies in this direction can bring out more facts about the prognosis.

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