Original Research Article

Correlation of Neutrophil to Lymphocyte and Monocyte to Lymphocyte Ratio with Acute Phase Reactant in Septicemia: A Prospective Study. NLR and MLR as Alternative in Sepsis

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Abstract

Introduction: Acute phase reactants (Procalcitonin, C-Reactive Protein) are important parameters in diagnosing and prognosticating sepsis. Despite availability of these, all the laboratories and hospitals are not equipped with the high end diagnostic capabilities in developing nations. Using alternative available markers in such conditions is preferable. We correlated the ratios from complete blood count with parameters procalcitonin and CRP.**Material and Methods:** This was a prospective study conducted in tertiary care hospital. All the patients admitted with diagnosis of sepsis who fulfilled the inclusion and exclusion criteria were included in this study. Venous sample were collected from all the patients. Complete blood count, procalcitonin and C reactive protein was done. Ratio of neutrophil to lymphocyte and monocyte to lymphocyte was calculated and correlated.**Results:** A total of 102 patients were included in this study. 49 were males and 53 females with an average age of 48.72 ± 11.21. The mean NLR was 14.09 ± 3.31 while mean MLR was 0.71 ± 0.15. Average procalcitonin was 25.38 ± 9.34 and the mean CRP was 142.97 ± 32.20. the correlation was checked using pearson's coefficient. There was a strong correlation between NLR with procalcitonin and CRP which was statistically significant (<0.001). MLR had a strong to moderate correlation with both the parameters and was statistically significant.**Conclusion:** Calculating the ratio of blood parameters from the complete blood count is the easy and cheap way to diagnose the sepsis in hospitals where high end clinical investigations are not available.

Keywords: NLR, MLR, Procalcitonin, Sepsis

Introduction

Sepsis is a systemic immunologic reaction by the body to any infectious process which can progress to end stage organ dysfunction. It remains one of the major causes of morbidity and mortality in critically ill patients [1]. The most common site of infection from which sepsis originates is lung, followed by the abdomen, bloodstream, urinary tract [2, 3].

Finding an appropriate biomarker of the immune response in sepsis, regardless of its cause is challenging. Many of these biomarkers have been studied in clinical setting with conflicting results. In this regard, complete blood count (CBC) has been investigated as a potential one with promising results. History of CBC dates back to 1852 and was first performed by Karl Vierordt [4, 5, 6, 7]. In patients with sepsis, conventional systemic inflammatory parameters include increased leucocytes (white blood cell count >12,000) or decreased leucocytes (WBC count <4,000).

CRP is a routine biomarker for infection and inflammation [8] that binds the phospholipid components of microorganisms which in turn facilitates its easy removal by macrophages. It is commonly used to screen for early onset sepsis because of its high sensitivity [9, 10].

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Procalcitonin (PCT) is the precursor of mature calcitonin, a hormone which reduces plasma calcium levels. It is a part of the systemic response that leads to severe sepsis. It may be elevated in a number of disorders in the absence of infection, especially following trauma. The cut off values for PCT used to determine the sepsis risk appear to be higher in patients who are critically ill. PCT levels may vary early during the development of sepsis and the test's predictive power is probably only significant later in the patient's course. Therefore, PCT levels should be monitored over time [11, 12].

The Neutrophil lymphocyte ratio (NLR) is simply calculated as the ratio of absolute values of neutrophils to lymphocytes. Monocyte to lymphocyte ratio (MLR) is similarly the ratio of absolute values of monocytes to lymphocytes. The way by which NLR elevates, is an intricate interplay of endogenous cortisol and catecholamines [13]. In sepsis there is death of lymphocytes so it may lead to increase in NLR [14]. NLR is not only increased in inflammation but it may get elevated in response to any physiologic stress. Therefore, it may help in differentiating severe illness from milder illness. Since NLR rises rapidly following acute stress, making NLR a preferable parameter of choice for acute illness as other parameters of the complete blood count, which take more time to increase. Steroids from outside can increase the NLR and on the other hand adrenal insufficiency may decrease it. For diagnosing severe sepsis or septic shock in patients, NLR was found to be a superior parameter when compared to C Reactive Protein and almost identical to procalcitonin [15]. Similar to NLR, Monocyte Lymphocyte Ratio (MLR) can be used to predict the course of many diseases leading to septicemia [16, 17, 18]. MLR had been studied in the past for its prognostic value in sepsis patients. It is

a good long term morbidity and mortality indicator in sepsis patients. MLR is useful in particularly diseases like Respiratory distress syndrome, tuberculosis, klebsiella pneumonia and other respiratory diseases leading to sepsis. The higher value in these patients was related to higher level of mortality as well as long term disability.
Our prospective observational study had been undertaken to assess the correlation of NLR and MLR ratio with acute phase reactants among patients of Septicemia as these markers were inexpensive and easy to perform as compared to CRP and procalcitonin.

Materials and Methods
The present study was a hospital based prospective observational study conducted in the Department of Pathology at a tertiary care hospital in north India from October 2020 to August 2022. Patients of age above 18 years with the diagnosis of sepsis admitted to the hospital in patient department were included. Patients with malignant disease of any origin and any preexisting immunodeficiency were excluded. After obtaining the patient consent, detailed history was taken and samples were collected for sepsis biomarkers which included complete hemogram, procalcitonin, CRP and blood cultures In all included patients, venous blood samples were taken into Vacutainer K3 EDTA tubes. A complete blood count was determined by the Yumizen 2500/Penta XLR haematology. Procalcitonin and C reactive protein were done using fluorescent immunoassay. All the data was collected and NLR, MLR were calculated on day 1, 3 and 5.

Statistical Analysis
Data were analyzed by SPSS (Statistical Package for the social service) software version 23. A p-value of less than 0.05 was considered statistically significant. All outcome variables were tested for normality. Parametric tests (Repeated Measures ANOVA) were used to make statistical inference as data were normally distributed. Parametric tests (Pearson's Correlation) were used to explore the correlation between the two variables as all were normally distributed.

Results
A total of 102 patients were included in this study after due consideration of inclusion and exclusion criteria. Out of 102, 49 were males and 53 were females. The mean Age (Years) was 48.72 ± 11.21 (Table 1).

Table 1: Demographic Details of patients

Basic Details	Mean ± SD
Age (Years)	48.72 ± 11.21
Gender	Male - 49 Female - 53

The mean Total Leucocyte Count (Cells/mm³) on Day 1 was 23.58 ± 2.73, on Day 3 was 18.00 ± 2.88 and on Day 5 was 11.74 ± 1.37. The mean Total Leucocyte Count (Cells/mm³) decreased from a maximum of 23.58 at the Day 1 to a minimum of 11.74 at the Day 5. This change was statistically significant (Repeated Measures ANOVA: F = 126.5, p = <0.001). The mean NLR decreased from a maximum of 14.09 at the Day 1 to a minimum of 8.11 at the Day 5. This change was statistically significant (Repeated Measures ANOVA: F = 61.3, p = <0.001). The mean MLR decreased from a maximum of 0.71 at the Day 1 to a minimum of 0.55 at the Day 5. This change was statistically significant (Repeated Measures ANOVA: F = 9.0, p = <0.001) (Table 2).

Table 2: Blood Parameters on Day 1, 3 and 5

Parameter	Day 1	Day 3	Day 5	P Value
Total Leucocyte Count	23.58 ± 2.73	18.00 ± 2.88	11.74 ± 1.37	<0.001
Neutrophil Lymphocyte ratio	14.09 ± 3.31	12.30 ± 2.74	8.11 ± 2.22	<0.0001
Monocyte Lymphocyte ratio	0.71 ± 0.15	0.68 ± 0.14	0.55 ± 0.14	<0.0001

The mean Procalcitonin (ng/mL) was 25.38 ± 9.34. The mean CRP (mg/dL) was 142.97 ± 32.20.
There was a strong positive correlation between NLR (Day 1) and Procalcitonin, and this correlation was statistically significant (r = 0.88, p = <0.001)(Fig 1). For every 1 unit increase in NLR (Day 1), the Procalcitonin (ng/mL) increases by 2.49 units (Table 3). There was a moderate positive correlation between NLR (Day 1) and CRP (mg/dL), and this correlation was statistically significant (r = 0.36, p = <0.001) (Fig 2).

Table 3: Correlation between NLR, MLR with procalcitonin and CRP

Correlation	Pearson's Correlation Coefficient	P Value
NLR (Day 1) vs Procalcitonin (ng/mL)	0.9	<0.001
MLR (Day 1) vs Procalcitonin (ng/mL)	0.5	<0.001
NLR (Day 1) vs CRP (mg/dL)	0.4	<0.001
MLR (Day 1) vs CRP (mg/dL)	0.3	0.006

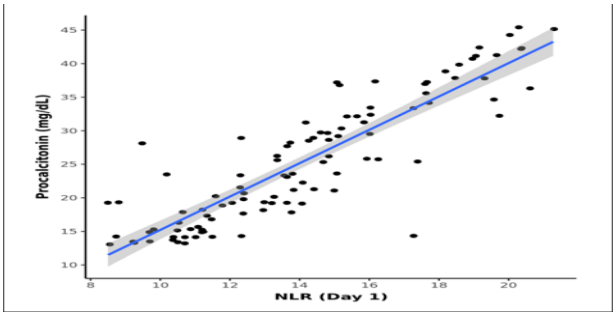

Figure 1: Correlation between NLR (Day 1) and Procalcitonin

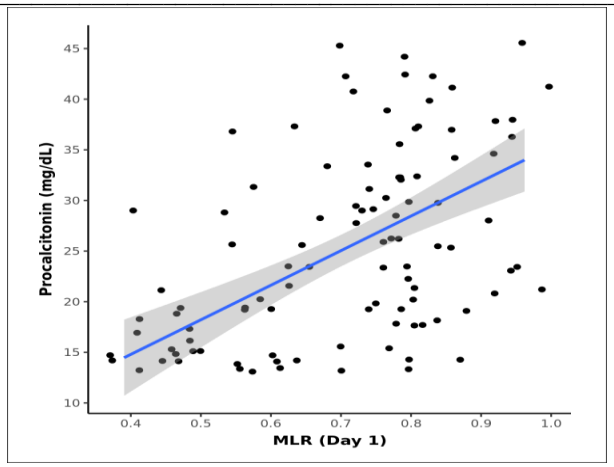

Figure 2: Correlation between MLR (Day 1) and Procalcitonin

There was a moderate positive correlation between MLR (Day 1) and Procalcitonin (ng/mL), and this correlation was statistically significant (r = 0.53, p = <0.001) (Fig 3). There was a weak positive correlation between MLR (Day 1) and CRP (mg/dL), and this correlation was statistically significant (r = 0.27, p = 0.006) (Fig 4).

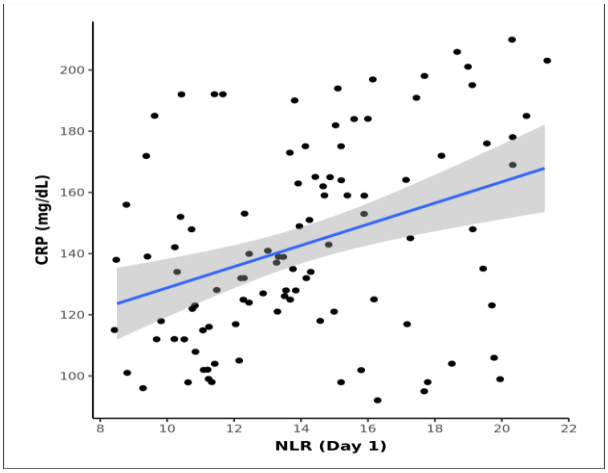

Figure 3: Correlation between NLR (Day 1) and CRP

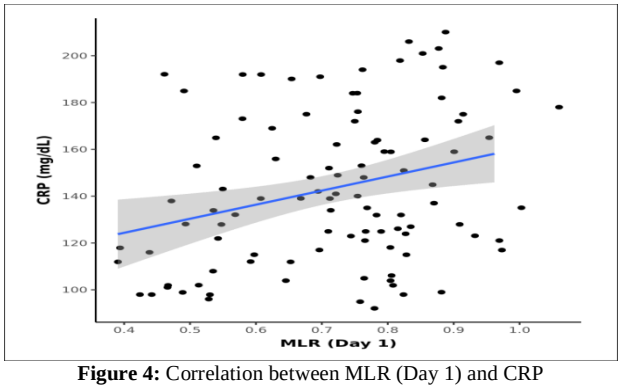

Figure 4: Correlation between MLR (Day 1) and CRP

Discussion

Sepsis is one of the most challenging aspects of health care which poses a big burden on society in terms of morbidity and mortality [3]. Sepsis biomarkers play an important role in diagnosing and managing the disease course. They are helpful in measuring the severity of the pathological process along with its impact on patient health in the future. There are numerous biomarkers for sepsis which include various parameters like complete hemogram, Erythrocyte sedimentation rate. C reactive protein and procalcitonin [7]. Many ratios from hemogram parameters had been studied and utilized as biomarkers in sepsis.

Neutrophil to Lymphocyte ratio, Monocyte to Lymphocyte ratio, Monocyte Distribution width, platelet to lymphocyte ratio, and others had been studied to find an easy and affordable alternative for the

setups which lack high end equipped laboratories.

In this study, procalcitonin and CRP were tested on day 1 of admission, NLR and MLR were calculated on days 1, 3, and 5. Values of NLR and MLR were compared with procalcitonin and CRP for finding the correlation as biomarkers for sepsis assessment. NLR and Procalcitonin were strongly correlated with each other and was statistically significant ($p < 0.001$). NLR was also compared with CRP. The Pearson's coefficient was 0.4 which was statistically significant($p<0.05$). however, the correlation value showed that it was moderately correlated as compared to procalcitonin.

The results provide a useful insight into the relationship of NLR with procalcitonin and CRP. The degree of positive correlation that is more than 0.6 shows that it can very well be used as a prognostic marker for good clinical outcomes. Similar results were also concluded in different studies [19, 20, 21, 22, 23].

The value of MLR on day 1 and procalcitonin was moderately correlated but were statistically significant. Pearson's Correlation coefficient was 0.5 which was statistically significant. Tian et al [24] stated a specificity of 87% for MLR in predicting the severity in sepsis patients compared to gold standard biomarkers but was not highly sensitive in predicting the outcome. Yang et al [25] used MLR ratio in predicting the mortality rate in respiratory distress syndrome patients with sepsis. The study concluded that the high MLR was associated with poor outcomes in sepsis patients ($p<0.001$). Huang et al [26] also reported high diagnostic performance of MLR in predicting sepsis when compared between two groups of community acquired pneumonia.

MLR was also correlated with CRP using Pearson's correlation method. Value was 0.3 on Day 1 which suggests a low correlation of MLR with CRP.

Conclusion

Sepsis Biomarkers play an important role in the diagnosis and prognosis of patients.

All the laboratories are not well equipped with high end analyzers for parameters like procalcitonin and CRP. The role of CBC parameters and leucocyte ratios are extremely helpful in areas where procalcitonin and CRP can not be done. NLR and MLR both were positively correlated with procalcitonin and CRP. However, NLR presented a very strong correlation and can be used as a substitute for procalcitonin in places where it is not available and is better correlated than MLR. Using both parameters together will increase the sensitivity of diagnosis and prognosis in such patients.

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