Original Article

Hematological Parameters as Morbidity and Mortality Predictors of Sepsis

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Abstract

Background : Diagnosing and treating Sepsis is a challenging situation. It becomes imperative to know about the factors that can deteriorate the situation further. Although there are biomarkers available for diagnosis and prognostication of Sepsis, yet they are time consuming and not readily available in resource limited settings. This study aims to find the role of Neutrophil Lymphocyte Ratio (NLR), Monocyte Lymphocyte Ratio (MLR) and Platelet Lymphocyte Ratio (PLR) as predictor of outcome in sepsis.

Material and Methods : This was an observational, prospective study where a total of 115 patients diagnosed with Sepsis by qSOFA >2 on admission or change in SOFA score >2 from baseline were included. The aim of study was to look for the role of Neutrophil Lymphocyte Ratio, Monocyte Lymphocyte Ratio and Platelet Lymphocyte Ratio as morbidity and mortality indicator in patients with sepsis.

Results : Platelet Lymphocyte Ratio (PLR) and Neutrophil Lymphocyte Ratio (NLR) were found to have maximum predictability of mortality (99.1%). Similarly, NLR and PLR were also found to be statistically significantly higher in those requiring Mechanical ventilation and Renal replacement therapy.

Conclusions : Both Neutrophil Lymphocyte Ratio and Platelet lymphocyte Ratio have been found to have positive correlation with the poor prognosis in case of Sepsis. They can be quite useful in the resource limited settings.

Key words : Neutrophil Lymphocyte Ratio (NLR), Monocyte Lymphocyte Ratio (MLR), Platelet Lymphocyte Ratio (PLR), All cause mortality, Vasopressors, Renal Replacement Therapy, Mechanical Ventilation.

The origin of the word "*Sepsis*" dates back to around 2700 years ago. Derived from greek word 'Sepsin'[1] which means "*To make putrid*".

Sepsis is defined as the body's dysregulated response to the presence of infection resulting in life threatening organ dysfunction[2]. Sepsis is clinically identified by an acute change in the SOFA score by more than 2 points in a patient with suspected bacterial infection[3].

Septic shock is defined as the condition where underlying circulatory, cellular and metabolic process in sepsis are profound enough to increase mortality[2]. Septic shock according to the Sepsis 3 criteria is defined as the need for vasopressors in a patient with sepsis to maintain MAP $\geq$ 65 mmhg or Lactate $\geq$2 mmol/L despite adequate fluid resuscitation[3].

Sepsis is often quite challenging to treat as well as to be diagnosed. Numerous clinical criteria for diagnosis of sepsis have come up over a period of time. It has evolved from Systemic Inflammatory Response Syndrome (SIRS) to q SOFA, (Sequential Organ Failure Assesment) SOFA, NEWS (National Early Warning Score), MEWS (Modified Early Warning Score) and APACHE. These scores can often be used to predict mortality and also provide therapeutic guidance. Apart from these clinical scores there are various Biomarkers also available for diagnosing sepsis, prognostication as well as to predict the response to antibiotics[4]. CRP and Procalcitonin are the ones most frequently used. CRP can be raised in both inflammatory and noninflammatory diseases. Procalcitonin, although a useful marker but is quite expensive and not readily available in the resource limited settings. In 2001, there was another marker recommended as an infection biomarker ie, Neutrophil Lymphocyte Ratio (NLR)[5]. Since then there has been a surge in investigating the role of other simple parameters derived from Complete Blood

Editor's Comment :

- Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) are simple, cost-effective biomarkers that strongly correlate with morbidity and mortality in sepsis.
- Elevated NLR and PLR values can assist clinicians in early risk stratification and prognostication, especially in resource-limited settings

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Count (CBC) which include besides NLR, Monocyte Lymphocyte Ratio (MLR), Platelet Lymphocyte Ratio (PLR) and Platelet count to mean platelet volume in various diseases in assessing the disease severity and association with mortality[6-10]. As these markers NLR, MLR and PLR are easy to obtain, cost effective, easily available in the resource limited settings , so this study aims to find the role of NLR, MLR and PLR as prognostic markers and also to find their correlation with CRP, Procalcitonin and Lactate.

Aims & Objectives

(1) To evaluate the role of Neutrophil Lymphocyte Ratio (NLR), Monocyte Lymphocyte Ratio (MLR) and Platelet Lymphocyte Ratio (PLR) as indicator of morbidity and mortality in patients with Sepsis.

(2) Correlation of NLR, MLR and PLR with the already existing markers of sepsis like C Reactive Protein, Procalcitonin and Lactate.

Material and Methods

Study Design :

This was an Observational, Prospective study conducted in a Tertiary Care Center in Dehradun.

Study Setting :

Consecutive patients were enrolled for the study for a period of 1 year after clearance from Institutional Ethical Committee.

Inclusion Criteria :

Patients aged >18 years with underlying infection and Sepsis diagnosed by q SOFA>2 at admission and change in SOFA score >2 from the baseline were included in the study.

qSOFA :

(1) Respiratory rate >22 breaths/min. (2) Altered mental status. (3) SBP<100mm hg

Exclusion Criteria :

Pregnant patients, Immunocompromised patients including HIV,

Those on Immunosupressants. Surgical patients with sepsis,

Those who died within 12 hours of hospitalisation. Those with underlying malignancies were excluded from the study.

Before enrolment, all patients (or their relatives if patient was in altered sensorium) were informed about the study and informed consent was taken.

Detailed history and physical examination was done of all those patients who were then enrolled in the study after screening for Inclusion and exclusion criteria. Patient's sensorium was evaluated by Glasgow Coma Scale which included Eye(E), Verbal (V) and Motor (M) response. Venous samples were then drawn and sent for Haematology, Biochemistry, Arterial Blood Gas Analysis, CRP and Procalcitonin. Paired samples were sent for Blood Culture/Sensitivity (both aerobic and anaerobic) and from other presumed sources of infection before initiating antibiotics. Chest X-ray and Ultrasonography Abdomen were done at the time of admission.

Other investigations like sputum examination, Pleural fluid, ascitic fluid or CSF analysis were also done in selected cases.

Patients were further categorized on the basis of source of infection like Sepsis (Genitourinary cause), Sepsis (Pulmonary cause), Sepsis (Abdominal cause) and Sepsis (Skin and Soft Tissue Infection cause).

Outcomes :

Primary Outcome :

To find the predictability of all cause hospital mortality in patients with altered Neutrophil Lymphocyte Ratio (NLR), Monocyte Lymphocyte Ratio (MLR) and Platelet Lymphocyte Ratio (PLR).

Secondary Outcomes :

To find the correlation of altered NLR, MLR and PLR with ICU stay and total duration of stay in hospital.

Statistical Analysis :

The data collected for the study included :

(1) General information : Name, age and sex of the patient, co-morbidities.

(2) Behavioural traits : Status of smoking and alcoholism.

(3) Laboratory parameters : Neutrophil Lymphocyte Ratio (NLR), Monocyte Lymphocyte Ratio (MLR), Platelet Lymphocyte Ratio (PLR), Total Leucocyte Count (TLC), Procalcitonin, CRP, Creatinine, Bilirubin, Lactate, SGOT, SGPT levels, blood culture, urine culture, Sputum Culture, Pus culture, Ascitic fluid culture, Pleural fluid culture.

(4) Clinical parameters : Glasgow Coma Scale (GCS), Heart Rate (HR), Mean Arterial Pressure (MAP), Respiratory Rate (RR).

(5) Hospitalization parameters : ICU stay, Total duration of stay.

(6) Diagnostic parameters : Source of infection, Tentative diagnosis.

(7) Other parameters : Status of administration of vasopressors, mechanical ventilation and Renal replacement therapy.

The collected data was analyzed in SPSSv28 software

Descriptive analysis was done for different parameters followed by Analysis of Variance (ANOVA) to determine the association of various clinical and other parameters on NLR, MLR and PLR. Correlation analysis was also performed to find out the correlation between NLR, MLR and PLR and different laboratory and hospitalization parameters. Predictability of sepsis outcome based on various parameters like NLR, MLR, PLR and their combinations was deduced using logistic regression and ROC curves were obtained for the most important parameters.

Results

A total of 156 patients were included in the study and subsequently 41 patients were excluded. Finally, 115 patients met the criteria for the study. Diagrammatic algorithm of the study population is shown in Fig 1.

Out of 115 patients, 75 patients survived and 40 patients expired. Various sources of infection in the study population were: Respiratory causes in 59 patients (51.3%), Genitourinary causes in 23 patients (20%), Abdominal causes in 17 patients (14.7%) and Skin and soft tissue infection in 16 patients (14%).

Maximum patients were found to have Pneumonia (54 patients, 46.9%) as cause of infection.

The mean age of the study population was 54.03±0.89 years with range of 27-70 years. There were 64.35% males and 35.65% females in the study population.

In the study population, the survived group and expired group were found to have various comorbidities. Diseases like T2DM, CAD, Hypertension and CKD were found to be higher in the Expired group; whereas diseases like T1DM, CLD, Bronchial asthma, COPD and TB were found only in the survived group.

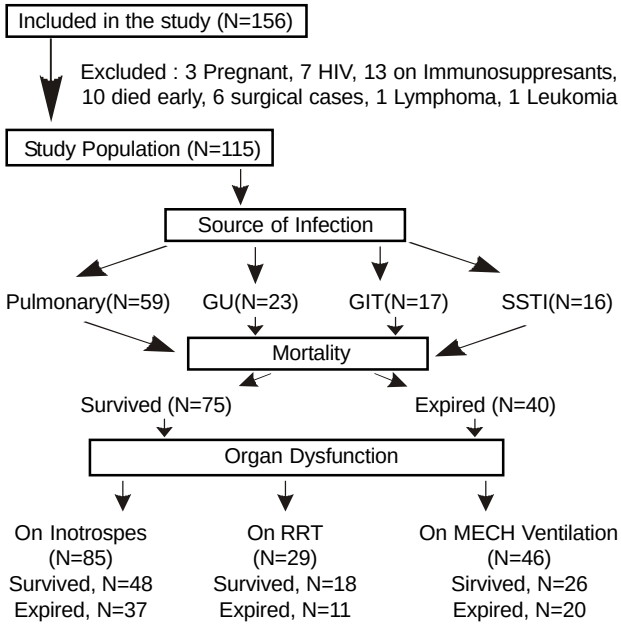

Fig 1 — Diagrammmatic Algorithm of the study population

It was found that the expired group had significantly higher mean Age, SOFA score, significantly lower sensorium as indicated by Glasgow Coma Scale (GCS) compared to the Survived group. Also, vitals like Heart Rate and Respiratory rate were significantly higher in the expired group, Mean Arterial Pressure was significantly lower in the expired group compared to the survived group. Other parameters like number of days in ICU and total duration of stay in the hospital were significantly lower in the expired group.

Also, the Laboratory parameters like Total Leucocyte Count (TLC), Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) had statistically significant higher values in the expired group than the survived group. Other investigations like Lactate levels, CRP, Procalcitonin, Creatinine and Bilirubin too had significantly higher mean in the expired group compared to the survivors (Table 1).

The primary outcome of the study, ie, predicting the all-cause mortality from the altered NLR, MLR and PLR individually as well as in combination, was calculated from the Chi-square test. We found that NLR and PLR in combination were having the maximum predictability (99.10%) of mortality due to sepsis followed by PLR and MLR in combination (97.4%).

Individually, PLR has the maximum predictability of 93.0% followed by NLR which has predictability of

Table 1 — *Effect of baseline parameters on the mortality*

Parameters	Study Population (N=115)	Survived (N=75) Mean±SE	Expired (N=40) Mean±SE
Age (in years)	54.03±0.89	52.05±1.02	58.38±1.39**
CRP(mg/dl)	74.85±1.79	64.29±1.52	94.13±2.07**
Procalcitonin(ng/ml)	9.54±0.22	8.31±0.19	11.89±0.25**
TLC (cells/cu.mm)	24204.43±690.1	20768.51±664.5	30691.00±903.8**
NLR	23.95±0.71	20.14±0.65	31.02±0.89**
MLR	0.72±0.02	0.69±1.55	0.89±1.11
PLR	265.59±7.47	213.76±4.59	359.35±6.24**
Lactate (mmol/L)	3.35±0.09	2.79±0.07	4.38±0.09**
Bilirubin (mg/dl)	1.72±0.09	1.71±0.15	2.00±0.21**
Creatinine(mg/dl)	2.37± 0.11	2.16±0.19	4.22±0.25**
GCS	9.97±0.17	11.18±0.09	7.73±0.12**
HR (beats/min)	135.09±0.84	129.49±0.56	145.30±0.77**
MAP (mm hg)	49.93±0.52	53.08±0.42	44.03±0.57**
RR (breaths/ min)	34.17±0.51	32.07±0.54	38.08±0.74**
ICU Stay (in days)	4.95±0.18	5.43±0.20	3.95±0.28**
Total Stay (in days)	7.55±0.35	9.19±0.32	4.45±0.44**
SOFA score	11±2	9±2	13±2**

** indicates p value ≤0.01

86.10%. Individually, MLR has the least predictability of mortality (68.70%). The AUC for NLR was 0.916 and that for PLR was 0.998 with p value of <0.001.

Secondary outcome of the study was to find the correlation of total duration of stay in hospital and duration of stay in ICU with the altered NLR, MLR and PLR. It was found that all the three parameters ie, NLR, MLR and PLR were found to be negatively correlated with the Duration of stay in ICU and total duration of stay in hospital and the difference was highly significant (Table 2).

The highest correlation was found for PLR with total duration (r=-0.688) and days in ICU (r=-0.488) followed by NLR with total duration (r=-0.534) and Days in ICU (r=-0.349).

Discussion

Sepsis still continues to be among the top 10 causes of mortality. In our study, 40 out of 115 patients ie, 34.78% patients died similar to the study by Kaushik R, *et al* who also found mortality of 33.9%[11]. One of the major cause of high mortality in Sepsis is because of delay in diagnosis and delayed initiation of treatment.

Table 2 — *Correlation of ICU stay and total duration of stay with NLR, MLR and PLR*

Parameters	ICU Stay	Total Stay
NLR	r = -0.349, p<0.001	r = -0.534, p<0.001
MLR	r = -0.296, p<0.001	r = -0.297, p<0.001
PLR	r = -0.488, p<0.001	r = -0.688, p<0.001

The major cause of Sepsis in the study population was found to be Pneumonia followed by Complicated UTI or Pyelonephritis. This is in consensus with the other similar studies done on Sepsis where Pneumonia is the topmost cause of Sepsis in hospitalised patients followed by Genitourinary infections[12-14].

Primary outcome ie, to find the predictability of all cause mortality from altered NLR, MLR and PLR showed that PLR and NLR in combination had the maximum predictability and individually, PLR was found to have maximum predictability of mortality followed by NLR. Spoto S, *et al* also found NLR and PLR to have a high positive predictive value of 96% for mortality in Sepsis[15]. Shen Y, *et al* also found that high PLR at admission was associated with the mortality in patients with Sepsis[16]. Huang Z, *et al* did a meta analysis of 14 studies to assess the role of NLR as a prognostic marker in patients of sepsis. They found that higher values of NLR were found in the non survivors compared to the survivors and hence concluded that NLR has a prognostic role in patients with Sepsis[17].

This is a commonly recognized fact that Sepsis is because of the immune dysregulation and it includes the role of both pro inflammatory and anti inflammatory markers[18]. The increase in NLR in Sepsis can be attributed to the increase in the neutrophils and apoptosis of lymphocytes in Sepsis and also due to some endogenous mediators like catecholamines and cortisol[19,20]. Platelets have a role as an immuno-modulatory agent by causing release of various cytokines and also by interacting with bacteria and various other inflammatory cells, hence resulting in the upregulation of the inflammatory process[21-24].

We also found the AUC of NLR in predicting mortality of 0.916 and AUC of PLR in mortality was 0.996. This is in contrast to the finding of Spoto S, *et al* who found AUC of NLR in predicting mortality as 0.661. However, they took only patients outside the ICU setting and also, they measured 90 day mortality, whereas in our study, only mortality during hospital stay was measured[15]. Findings similar to our study were also reported by Kaushik R, *et al* who found a significantly high AUC of NLR as 0.911 in the early phase of sepsis as compared to the control population[11].

We also found an inverse correlation of NLR and PLR with the total duration of stay in hospital and days in ICU which can be explained by the fact that the patients in the expired group had high NLR and PLR and at the same time, lesser days of stay compared to the survived group. There have been studies in literature where a positive correlation of NLR, MLR and PLR was found with duration of stay in hospital but they were mostly done on diseases other than sepsis where immediate mortality is not comparatively high[25-28].

Other parameters like the need for Inotropes, need for Invasive mechanical ventilation and the need for RRT were found to have a strong correlation with NLR, MLR and PLR. Sari, *et al* also found Invasive mechanical ventilation use among those with high NLR and also who died within the first 5 days of admission[14].

CRP and Procalcitonin are the biomarkers that have been studied extensively in the sepsis followed by other biomarkers like IL 6, Presepsin and CD 64[4]. These markers have role not just for diagnostic purpose but also for prognostication and therapeutic decisions.

Gurol G, *et al* evaluated the CRP, Procalcitonin, WBC and NLR in patients with sepsis and they found that NLR had the best predictive value among all. They also found that CRP and Procalcitonin showed a correlation with NLR[29]. This is in concordance with our study where both NLR and PLR were found to have a strong positive correlation with CRP, Procalcitonin and Lactate.

Conclusion

Hence, we would like to conclude that NLR and PLR have a role as predictor of mortality and morbidity in patients of Sepsis. Higher values of NLR and PLR are associated with the poor outcomes. But, further follow up studies need to be done to see their role in guiding therapeutic decisions.

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Conflict of Interest : None.

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