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ASSOCIATION BETWEEN PLATELET-TO-LYMPHOCYTE RATIO, NEUTROPHIL-TO-LYMPHOCYTE RATIO, MONOCYTE-TO-HDL CHOLESTEROL RATIO AND LIPID PROFILE PARAMETERS IN SEPSIS - A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Background: Sepsis is a global health issue and a medical emergency that requires timely intervention. Early diagnosis and prediction of severity are very essential to reduce the mortality in sepsis. Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR) and Monocyte-HDL Ratio (MHR) can be easily calculated from the Complete Blood Count (CBC) values and lipid profile and are relatively less expensive which can be used to predict the outcome of sepsis. We aimed to study the association between these parameters and the clinical outcomes of patients with sepsis. **Methodology:** We have conducted a prospective observational study including 80 study participants from medical and surgical ICUs. Among them, 59 survived and 21 patients expired. Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR) and Monocyte-to-HDL Ratio (MHR) were calculated. SOFA score was also calculated at two intervals one during admission and on day 5. All the parameters were compared between the survivors and the non-survivors. **Results:** In both Survivors & Non-survivors, NLR, PLR and MHR ratio, Total cholesterol and LDL – C were elevated HDL – C showed a significant decrease on Day 5 (23.88 ± 10.19 vs 16.67 ± 8.27 mg/dl). In Non-survivors, NLR, PLR & MHR showed a significant increase on day 5, and HDL- C

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showed a significant decrease on day 5. In Non survivors HDL – C showed a negative correlation with NLR & PLR. **Conclusion:** Our study suggests that NLR, PLR and MHR are promising predictors of inflammatory and oxidative stress in sepsis. Hence, NLR, PLR and MHR can be used as cost-effective clinical predictors in patients with sepsis.

Keywords: Sepsis, SOFA score, HDL Cholesterol, Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR), Monocyte-to-HDL Ratio (MHR).

Introduction

Sepsis is a "life-threatening organ dysfunction caused by a dysregulated host response to infection". Sepsis is a major cause of in-hospital morbidity and mortality, which accounts for almost 20% of deaths worldwide[1]. Recent global estimate reports approximately 49 million sepsis cases and 11 million sepsis-related deaths worldwide[2].

Until now, Blood culture remains the reference test for diagnosing sepsis. Increased turn-around time and low sensitivity limit its use in emergency conditions. Since sepsis is a potentially fatal disease, it is very crucial to diagnose and initiate anti-microbial therapy to reduce mortality. Even though Procalcitonin (PCT) is a widely used prognostic marker, its high cost limits its usage in all healthcare settings. It necessitates looking for alternate, cost-effective biomarkers that can predict the outcome of sepsis.

Lipoproteins have pleiotropic effects in immune regulation besides their well-defined role in metabolism. Lipoproteins are considered protective factors in sepsis, as they can neutralize bacterial toxins due to their potential immunomodulatory properties. Decreased High-Density Lipoprotein (HDL-C) is generally associated with increased mortality in sepsis patients[3]. Hypocholesterolaemia and hypertriglyceridemia are used as predictors of mortality in sepsis[4,5].

Complete Blood Count (CBC) metric biomarkers like Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR) and Monocyte-to-HDL Ratio (MHR) are simple valuable tools in the monitoring of sepsis[6].

The simultaneous marked increase in neutrophil count and deep decline in lymphocyte count was observed in sepsis patients. Neutrophil-Lymphocyte Ratio (NLR) would be the optimal index to express the relationship between dynamic changes of neutrophils (innate immune cells) and lymphocytes (adaptive immune cells). Serial monitoring of NLR may warn clinicians about the severity of ongoing pathological processes and clinical consequences earlier. NLR is a rapidly available, cheaper, and valid immune response marker widely used across all medical disciplines[7]. It has been postulated that during sepsis, there is an interaction between inflammation and coagulation processes which leads to activation of platelets which in turn can aggravate the inflammatory reactions and associated coagulation abnormalities leading to clinical consequences of sepsis[8]. Lymphopenia along with elevated Platelet levels can lead to elevated Platelet-Lymphocyte Ratio (PLR) which can be used as an integrated reflection of enhanced host thrombotic/inflammatory response associated with high mortality rate in sepsis[9]. One of the important contributing factors in the pathogenesis of sepsis is oxidative stress. High circulating monocytes and low HDL-C expressed as Monocyte to HDL ratio (MHR) is a recently defined parameter of systemic inflammation and oxidative stress in various diseases[10]. In our study, we aimed to study the association between NLR, PLR, MHR

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and lipid parameters like Total Cholesterol, Triglycerides and HDL – Cholesterol in patients diagnosed with sepsis.

Materials And Methods

Patients and Methods

We have conducted a prospective observational study in the Department of Biochemistry after approval from the Institutional Ethics Committee. We have followed the ethical principles for medical research involving human subjects, in accordance with the Declaration of Helsinki of 1975, revised in 1983. The study participants were recruited from the medical and surgical ICUs from June 2022 to September 2022. 80 patients diagnosed with sepsis for varying causes have been included as study participants after subjecting to inclusion and exclusion criteria. The written informed consent was obtained from the patients or their legal guardians, after explaining the study protocol.

Inclusion criteria

Patients above 18 years of age and satisfy the criteria for diagnosing sepsis, as per international guidelines for the management of sepsis and septic shock[11].

Exclusion criteria

Pediatric patients, pregnant and lactating women, patients who died within 24 hours of admission or patients who were referred to another hospital, sepsis patients with HIV, malignancy, autoimmune diseases like systemic lupus erythematosus & rheumatoid arthritis and patients on immunosuppressive therapy, sepsis patients with dyslipidemia and patients on statin therapy.

Study Procedure

From all the study participants, a detailed medical history of presenting complaints and past history of prolonged illness and hospitalization were recorded. After a thorough clinical examination, the cause of ICU admission was recorded for each patient. SOFA score was calculated for all the patients using an online calculator[12] & Blood samples were collected and analyzed for Complete blood count, Lipid profile and serum procalcitonin on day 0 & day 5. All the study participants were followed throughout the study and the final status as discharged or deceased was obtained from the medical records department. Serum Total Cholesterol was estimated by the CHOD- PAP (Cholesterol oxidase & Peroxidase) method; Serum HDL – Cholesterol was estimated by selective inhibition method; Serum Triglyceride by GPO-TOPS (Glycerol-3-phosphate Oxidase & Peroxidase) method. All these parameters were measured using TBA 120 FR, a fully automated chemistry analyzer. During analysis, laboratory standard operating procedures were followed with internal quality control materials. Other lipid parameters like LDL & VLDL were calculated from Total cholesterol, Triglyceride & HDL levels by using Friedewald's formula. Complete blood count (CBC) was measured using Beckmann Coulter LH 750 Haematology analyzer. From the CBC values and lipid profile values, our study parameters NLR, PLR and MHR have been calculated.

Statistical analysis

All the study variables were expressed as Mean ± Standard Deviation or Median (Inter-Quartile Range). Kolmogorov-Smirnov test was used to check for normal distribution. Paired t-test and Wilcoxon signed-rank test were used to find the differences in the serum levels of

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lipid parameters, NLR, PLR, MHR and SOFA scores on day 0 and day 5 of admission. Differences in the study parameters between survivors and non-survivors were measured by Unpaired t-test or Mann-Whitney U test. Spearman correlation was done to evaluate the association between study parameters and SOFA score. All statistical analyses were done using SPSS version 23.0. p value < 0.05 is considered as statistically significant.

Results

95 study participants diagnosed with sepsis were included in the study. Out of 95 study participants, 9 were deceased before 5 days of admission and Triglycerides were more than 400 mg/dl in 6 participants. After excluding a total of 80 patients were included in this prospective study. All these participants were followed throughout the study period and their final status was identified. Out of 80 patients, 59 (74%) were survivors and 21 (26%) were non-survivors.

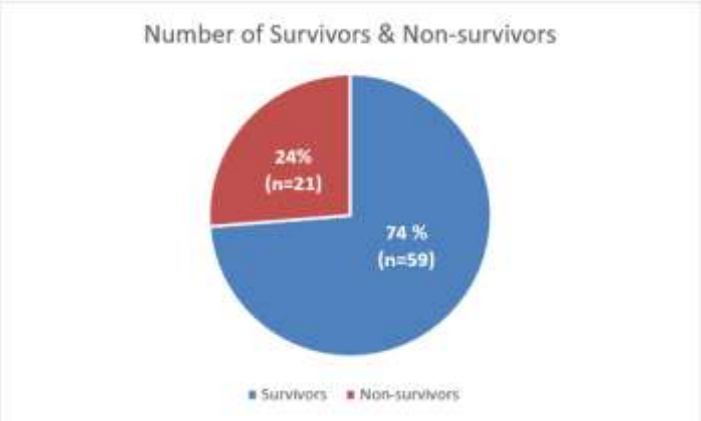

Figure 1: Distribution of Survivors and Non-survivors (n=80)

The biochemical and hematological indices were compared between the two groups on both day 0 and day 5. The correlation between the various study parameters was studied. Table – 1 shows the distribution of demographic details for both survivors and non-survivors.

Table 1: Distribution of demographic details for both survivors and non-survivors (n=80)

Age of the Patient	Male (n=56)	Female (n=24)	Number of patients (n=80)
18-30	6	2	08 (10.0%)
31-50	15	5	20 (25.0%)
51-60	14	8	22 (27.5%)
61-70	13	5	18 (22.5%)
71-80	8	4	12 (15.0%)

In both Survivors & Non survivors, HDL- C was significantly lower on day 5 compared to day 0. Whereas, SOFA score, NLR, PLR and MHR ratio, Total cholesterol and LDL – C were elevated on day 5 (Table 2) (Figure 2)

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Table 2: Difference in Study Parameters on Day 0 & Day 5 of admission – Paired t-test (Parametric test) / Wilcoxon signed-rank test (non-parametric test) – Both Survivors & Non-survivors

Parameters	Day 0	Day 5
Total cholesterol (mg/dL)	109.83±38.169	120.16±39.391
Triglycerides (mg/dL)	157 (104-208)	164 (114-225)
HDL - Cholesterol (mg/dL)	24.60±12.194	21.99±10.186
LDL - Cholesterol (mg/dL)	55 (30-71)	59 (43-81)
SOFA	3 (1-8)	4 (2-9)
NLR	9.06 (5.11-14.25)	13.95 (7.07-23.19)
PLR	18.46 (10.35-35)	25.43 (14.92-53.29)
MHR	0.23(0.13-0.41)	0.33(0.21-0.51)

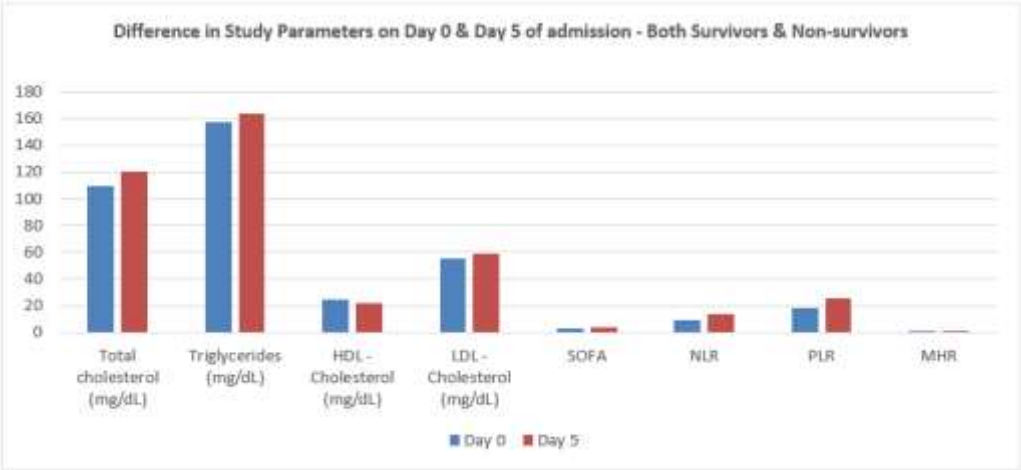

Figure 2: Difference in Study Parameters on Day 0 & Day 5 of admission - Both Survivors & Non-survivors

In survivors, Total cholesterol levels, SOFA scores, NLR, PLR & MHR were significantly higher on day 5 compared to day 0. LDL-C was lower significantly on day 5 compared to day 0. HDL–C was decreased on day 5 but not statistically significant (Table 3).

Table 3: Difference in Study Parameters on Day 0 & Day 5 of admission – Paired t-test (Parametric test) / Wilcoxon signed-rank test (non-parametric test) – In Survivors

Parameters	Day 0	Day 5	p-value
Total cholesterol (mg/dL)	108.29±37.299	123.59±39.304	0.005*
Triglycerides (mg/dL)	159 (107-212)	148 (115-230)	0.339
HDL - Cholesterol (mg/dL)	25.25±12.406	23.88±10.190	0.315
LDL - Cholesterol (mg/dL)	52 (44-86)	55 (29-69)	0.008*
SOFA	3 (1-4)	4 (1-6)	0.006*
NLR	9.17 (4.76-15)	13.4 (6.84-23.44)	0.001*
PLR	18.46 (9.97-63.6)	25.21 (14.9-42.14)	0.015*
MHR	0.21 (0.13-0.36)	0.30 (0.17-0.45)	0.001*

*p values < 0.05 are considered statistically significant.

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In non-survivors, among the lipid profile parameters, only HDL-C showed a significant decrease on day 5 compared to day 0. However, the haematological indices NLR, PLR & MHR showed a significant increase on day 5 compared to day 0 (Table 4) (Figure 3).

Table 4: Difference in Study Parameters on Day 0 & Day 5 of – Paired t-test (Parametric test) / Wilcoxon signed-rank test (non-parametric test) – In Non-Survivors

Parameters	Day 0	Day 5	p value
Total cholesterol (mg/dL)	114.14±41.153	110±38.947	0.654
Triglycerides (mg/dL)	154 (79-149)	115 (76-143)	0.139
HDL - Cholesterol (mg/dL)	23 (13-30)	15 (10-23)	0.019*
LDL - Cholesterol (mg/dL)	48 (36-78)	58 (33-86)	0.499
SOFA	4 (4-8.5)	4 (3-7)	0.337
NLR	8.96 (7.08-12.06)	18.51 (9.23-23.16)	0.024*
PLR	18.68 (11.93-38.57)	25.65 (13.27-65.11)	0.048*
MHR	0.33 (0.18-0.47)	0.57(0.32-0.76)	0.00634*

*p values < 0.05 are considered statistically significant.

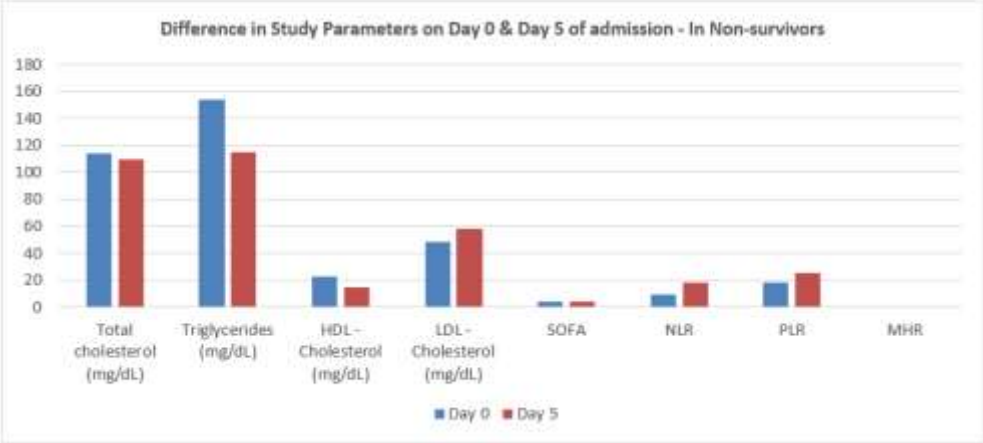

Figure 3: Difference in Study Parameters on Day 0 & Day 5 of admission - In Non-survivors

Spearman correlation between the lipid profile parameters and other study variables showed a significant positive correlation of triglyceride with SOFA scores and a negative correlation with PLR ratio in both survivors and non-survivors. HDL – C showed negative correlation with SOFA scores and PLR ratio (Table 5)

Table 5: Correlation of Lipid profile parameters with Haematological Parameters on Day 0 & Day 5 of admission- Spearman correlation (non-parametric test) – Both Survivors & Non-Survivors

Study parameter	Correlation Parameters	Day 0		Day 5	
		r value	p-value	r value	p-value
Triglycerides	SOFA	0.415**	0*	0.237*	0.034*
	NLR	-0.128	0.258	-0.173	0.125

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	PLR	-0.249*	0.026*	-0.234*	0.038*
HDL	SOFA	-0.261*	0.019*	-0.245*	0.029*
	NLR	0.195	0.084	0.037	0.748
	PLR	-0.298**	0.007*	0.276*	0.014*

* Correlation is significant at the 0.05 level (2 - tailed)

In Non survivors, Total cholesterol showed positive correlation with NLR whereas Triglycerides showed positive correlation with SOFA score on day 0. HDL – C showed negative correlation with NLR & PLR whereas LDL- C showed positive correlation with NLR (Table 6).

Table 6: Correlation of Lipid profile parameters with other study parameters on Day 0 & Day 5 of admission- Spearman correlation (non-parametric test) – In Non-Survivors

Study parameter	**Correlation Parameters**	**Day 0**		**Day 5**	
		r value	**p value**	**r value**	**p value**
Total Cholesterol	SOFA	0.287	0.206	0.196	0.395
	NLR	0.553**	0.009*	-0.179	0.437
	PLR	0.365	0.104	0.049	0.834
Triglycerides	SOFA	0.442*	0.045*	0.398	0.074
	NLR	-0.127	0.582	-0.027	0.909
	PLR	0.213	0.354	-0.194	0.399
HDL	SOFA	-0.106	0.648	-0.265	0.246
	NLR	-0.635**	0.002*	-0.050	0.830
	PLR	-0.599**	0.004*	0.362	0.107
LDL	SOFA	0.259	0.257	-0.015	0.949
	NLR	0.507*	0.019*	-0.172	0.455
	PLR	0.363	0.106	-0.018	0.940

Discussion

Sepsis is the most important life-threatening condition in India, which is more prevalent in males, predominantly in advanced age groups with co-morbidities and in patients with suppressed innate and adaptive immunity[13]. In the present study, we found that the age group from 31-50 years (22.45%) was more exposed to infection when compared to other age groups. Ahuja et al. have recorded that 52.3% of mortality was shown in ICU patients with hospital-acquired sepsis as well as organ dysfunction[14]. One of the important mainstays in treating sepsis and septic shock is the prediction of mortality. Various biomarkers have been evaluated to predict the outcomes in sepsis. In recent years, various studies have reported the role of platelets in immunomodulatory and inflammatory processes[15,16]. It has been postulated that sepsis and severe injuries result in apoptosis-mediated lymphopenia. The severity and duration of lymphopenia are associated with poor clinical outcomes. The imbalance between platelets and lymphocytes will be reflected in the Platelet-to-Lymphocyte Ratio. The higher PLR indicates the imbalance between pro-inflammatory and anti-inflammatory response by the host leading to worsening of clinical outcome in sepsis[17]. In our study, non-survivors showed an increase in PLR compared to survivors on day 5 of sepsis. In a retrospective study

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conducted by Shen Y et al, high PLR was associated with poor survival in sepsis patients[18]. A similar association was documented in neonates by Can E et al. A positive correlation was identified with PLR and early onset sepsis in term neonates[19]. In the early stages of sepsis, it has been documented that Neutrophil levels increase as a response to innate immunity and a decline in lymphocyte count due to the associated lymphocyte apoptosis[20]. These two processes would lead to elevated neutrophil-to-lymphocyte ratio (NLR). A cross-sectional study conducted by Rehman F U et al, NLR was found to be associated with the onset and severity of sepsis[8]. In our study, NLR was elevated significantly on day 5 both in survivors and non-survivors. Whereas in Non-survivors the levels are significantly higher compared to survivors [18.51 (9.23-23.16) vs 13.4 (6.84-23.44)]. One of the important contributors to the progression of sepsis is oxidative stress[21]. During the phase of oxidative stress, monocytes and HDL – C will oppose each other. Monocytes will be an important source of pro-inflammatory and oxidative mediators while HDL will inhibit the activation of monocytes. By combining these two effects, MHR shall be a precise parameter reflecting the anti-inflammatory and antioxidant effects[22]. Elevated MHR has been associated with unfavourable outcomes indicating systemic inflammation. In our study, MHR was higher on day 5 in non survivors indicating the poor outcomes in sepsis.

Limitations

First, the dietary habits and the nutritional status of the study participants were not taken into consideration which may influence the lipid profile status. Second, a multicentric study with a large sample size, taking uniform samples in both survivors and non-survivor groups may provide additional information about the exact role of these haematological indices in predicting the outcome of sepsis.

Conclusion

Our study suggests that NLR, PLR and MHR are promising predictors of inflammatory and oxidative stress in sepsis. A higher value of these parameters possibly predicts the mortality of sepsis patients. Hence, NLR, PLR and MHR can be used as cost-effective clinical predictors in patients with sepsis.

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