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ABSTRACT

CORRELATION OF SYSTEMIC IMMUNE-INFLAMMATION INDEX (SII) AND FERRITIN TO LYMPHOCYTE PERCENTAGE RATIO (FLPR) WITH NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) AMONG PATIENTS WITH SEVERE COVID-19: A RETROSPECTIVE OBSERVATIONAL STUDY FROM INDIA

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Objective: Coronavirus disease 2019 (COVID-19) causes multiorgan dysfunction due to hyperinflammation, dysregulated immune response and cytokine storm. Throughout the COVID-19 pandemic, a number of inflammatory biomarkers, including the neutrophil to lymphocyte ratio (NLR), have been investigated. The aim of this study is to assess the correlation of systemic immune-inflammation index (SII) and ferritin to lymphocyte percentage ratio (FLPR) with neutrophil to lymphocyte ratio among patients with severe COVID-19.

Methods: This retrospective observational study was conducted between May 2020 and August 2020 among 55 adult patients (males=35, 65%; females=19, 35%) admitted to intensive care unit (ICU) with severe COVID-19. Neutrophil to lymphocyte ratio (NLR), ferritin to lymphocyte percentage ratio (FLPR), systemic immune-inflammation index (SII) was calculated. Correlation of SII index, FLPR with NLR among severe COVID-19 patients was assessed. Outcome studied was death or recovery and discharge from the hospital.

Results: Majority were aged >65 years (n=22, 40%), and diabetes mellitus (DM) was the predominant comorbidity present (n=36, 65.5%). Mean peripheral oxygen saturation (SpO2) on ambient air at admission was 86.8%, mean days of illness from the symptom onset to hospitalization was 6.05 days and average length of stay was 16.22 days. NLR, mean±SD value was 10.17±12.32 and mean value of serum ferritin was 571.27±920.13 (ng/mL). The median (interquartile range, IQR) value of the SII was 1439.17(575.06-3802.05), and median (IQR)

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value of FLPR was 28.73 (12.79-62.02). We found statistically significant correlation between SII and NLR (r=0.926, p=0.0005), FLPR and NLR (r=0.580, p=0.0005) among patients with severe COVID-19. Twenty-six patients recovered (47.3%) and 29 patients died (52.7%).

Conclusion: SII and FLPR correlate significantly with most validated inflammatory marker NLR among patients with severe COVID-19.

Keywords: Coronavirus disease 2019, ferritin to lymphocyte percentage ratio, systemic immune-inflammation index, neutrophil to lymphocyte ratio.

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INTRODUCTION / ВСТУП

Coronavirus disease 2019 (COVID-19) is caused by an enveloped RNA beta coronavirus known as severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). COVID-19 pandemic was the biggest challenge and threat faced by healthcare systems globally and a race against time was witnessed in engineering effective vaccines for decreasing the spread, disease severity and death. As of April 4, 2024, 775 million cases have been reported worldwide including seven million deaths [1]. SARS-CoV-2 virus can virtually affect any organ system due to the expression of angiotensin-converting enzyme 2 (ACE2) receptor in most of the tissues resulting in devastating effects. ACE2 acts as a functional receptor for SARS-CoV-2 virus. Cellular entry of the virus is by means of attaching to ACE2 via receptor binding domain (RBD) of spike (S) protein [2]. The type 2 transmembrane serine proteases (TMPRSS2) facilitate viral entry into the cell by causing cleavage of spike protein and it also contributes to immune evasion. RBD and TMPRSS2 both play a role in evading immune surveillance [3]. Inflammation plays a key role in immunopathogenesis, severity of disease, critical illness and fatality in COVID-19. Immune response and inflammation should get suppressed when the SARS-CoV-2 is no longer a threat. Instead, in some patients, immune system goes overboard resulting in hyperinflammatory response and/or cytokine storm. Robust dysregulated inflammatory response is known to be associated with severe disease, critical illness and adverse outcomes in COVID-19 [4]. Severe COVID-19 is characterized by rise in inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) [5,6]. Various serological biomarkers of inflammation shown to be elevated in COVID-19 include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, procalcitonin. Increase in neutrophil percentage with lymphopenia is a cardinal feature associated with severe disease. Neutrophil to lymphocyte ratio (NLR) is the most validated marker in COVID-19 predicting disease severity and prognosticating disease outcomes [7]. Systemic immune-inflammation index (SII) (platelet multiplied by NLR) is an inflammatory marker extensively studied in solid organ malignancies for its association with outcomes [8]. Significantly higher ferritin levels and profound lymphopenia are seen in severe COVID-19 compared to those with mild/moderate disease suggesting adverse outcomes could be due to SARS-CoV-2 driven hyperinflammation [9]. Research has evaluated ferritin levels and lymphocyte count in relation to the severity of COVID-19 independently. Ferritin to lymphocyte percentage ratio (FLPR) may therefore be a unique inflammatory marker in COVID-19. There aren't enough studies on how the SII and FLPR relate to the NLR in COVID-19. The purpose of this study is to find the correlation of SII, FLPR with well validated inflammatory marker NLR among severe COVID-19 patients.

MATERIALS AND METHODS

This study aims to find the correlation of systemic immune-inflammation index (SII) and ferritin to lymphocyte percentage ratio (FLPR) with neutrophil lymphocyte ratio (NLR) among hospitalized patients with severe COVID-19.

This is a retrospective study conducted on patients admitted during the first wave of COVID-19 pandemic between May 2020 and August 2020 in a tertiary care hospital's intensive care unit (ICU) in south India which was designated for COVID care. Patients aged >18 years with severe COVID-19 were included in the study. All severe COVID-19 patients who were confirmed virologically by real time polymerase chain

reaction (RT-PCR) in a nasopharyngeal swab admitted to the ICU were included in this study. Severe COVID-19 is defined as patients with pneumonia and peripheral oxygen saturation (SpO2) ≤ 90% on ambient air, or respiratory rate > 30/min, or with signs of respiratory distress as per ministry of health and family welfare (MOHFW), India. Exclusion criteria include patients with mild and moderate COVID-19. Institutional ethics committee (IEC) approval was obtained with waiver of informed consent (No:75/53, august 2020) for the study. Ethical standards for human subjects laid down in Helsinki declaration were followed in conducting the study.

Data collection

Details of demographic data, presence of comorbid illness, clinical characteristics including symptomatology, admission SpO2 in ambient air, day of illness at hospitalization, length of hospital stay were collected for all the enrolled patients from the physical case records and entered in a study template proforma. Hemogram, serum creatinine (mg/dL), inflammatory markers which include c-reactive protein (CRP, mg/dL), serum ferritin levels (ng/ml), serum lactate dehydrogenase (LDH, U/L) and D-dimer (µg/mL) values at hospitalization were noted from the centralized database for laboratory reports portal in the health information management system. Neutrophil to lymphocyte ratio (NLR), ferritin to lymphocyte percentage ratio (FLPR) was calculated using the complete blood count and serum ferritin values. Systemic immune-inflammation index (SII) was derived based on the following formula, SII= [Platelets (10^9/L) x Neutrophils(10^9/L)]/Lymphocytes (10^9/L). NLR is well validated inflammatory marker for disease severity in COVID-19. Correlation of SII index and FLPR with NLR among severe COVID-19 patients was assessed. Outcome studied was death or recovery and discharge from the hospital. Association of various inflammatory markers like CRP, ferritin, LDH, NLR, FLPR, SII with hospitalization outcome were studied.

Data analysis/statistical analysis

The collected data was entered in the Microsoft Excel 2016 and analysed with IBM SPSS Statistics for Windows, Version 29.0 (Armonk, NY: IBM Corp). Descriptive statistics were used for describing the data; frequency analysis, percentage analysis was used for categorical variables and the mean, median, IQR (interquartile range) & SD (standard deviation) were used for continuous variables. The normality of the data was verified with Shapiro Wilk's test which showed the data was skewed, hence to find the significant difference between the bivariate samples in independent groups the Mann-Whitney U test was used. To assess the relationship between the variables FLPR and NLR, SII index and NLR, Spearman's rank correlation was used. P value <0.05 was considered as statistically significant.

RESULTS

Our cohort included a total of 55 adult patients with severe COVID-19 who were admitted to the ICU. Twenty-two patients were aged > 65 years (40%) and 9% were aged between 18yrs and 40yrs (n=5), with ages ranging from 22 to 93 years. Of the total 55 patients, 65% were males (n=35). Comorbid illness observed include diabetes mellitus (DM), systemic hypertension (SHT), coronary artery disease (CAD), pre-existing lung disease, chronic kidney disease (CKD), stroke, hypothyroidism, malignancy, venous thrombotic events in past. Of these, diabetes mellitus was predominantly seen (n=36, 65.5%) followed by systemic hypertension (n=26, 47.3%). About one-fourth (n=14, 25%) of all patients had at least one comorbidity each. Multimorbidity (>1 comorbid illness) was seen in 60% (n=33) of severe COVID-19 patients. Presence of 2 comorbid illness was observed in 34.5% (n=19), 3 comorbid conditions in 16% (n=9), 4 comorbidities in 7% (n=4) and one patient was noted to have 5 comorbid illness. Eight patients (14.5%) had no underlying comorbid conditions. Among the varied symptomatology in COVID-19, 82% had fever as the most common symptom (n=45), followed by dyspnoea in 60% (n=33). Table 1 shows the baseline characteristics of the study cohort.

Mean peripheral oxygen saturation (SpO2) on room air at admission was 86.8%, lowest SpO2 observed was 40% and median SpO2 noted was 88%. Mean days of illness from the symptom onset to hospitalization was 6.05 days. Average length of stay was 16.22 days, and observed maximum duration of stay was 52 days. Eosinopenia defined as eosinophil count less than 1% was noted in 87% of severe COVID-19 patients (n=48). Absolute eosinopenia of zero eosinophil percent on admission was seen in 36% (n=20). Table 2 shows the various inflammatory biomarkers in severe COVID-19 patients. Lymphopenia defined as lymphocyte count <25% (normal range of lymphocytes, 25-40%) was noted among 91% of severe COVID-19 patients (n=50), with lowest being 1.4% [lymphocytes = 0.22 x 10^9/L)]. Elevated neutrophils >70% of the total white blood cell count is termed as neutrophilia. 73% of study patients had neutrophilia (n=40) with maximum observed absolute neutrophil count being 37840 cells/µL. Thrombocytopenia (<100 x 10^9/L) was seen in three patients (5.45%), the lowest platelet count observed being 60x10^9/L. NLR more than 3 was seen in 78% (n=43) of severe COVID-19 patients and the highest NLR recorded in our study was 68.36. NLR less than 3 was seen in 12 patients (22%). Among the total cohort of 55 patients with severe COVID-19, 35% (n=19) had serum ferritin >500ng/ml, 98% (n=54) had LDH >245U/L and 44%

(n=24) had D-dimer >1 µg/mL. Among the various inflammatory biomarkers in COVID-19, elevated serum LDH levels >245U/L were observed nearly in all of the severe COVID-19 patients in our study; the highest value recorded was 1719U/L.

Table 1 – Baseline characteristics of severe COVID-19 patients

S.no	Parameter	Value
1.	Age (in years)	61.58±15.23
2.	Gender	
	- Male, n (%)	35 (65%)
	- Female, n (%)	19 (35%)
3.	Comorbidities, n (%)	
	- Diabetes mellitus	36 (65.5%)
	- Systemic hypertension	26 (47%)
	- Any underlying lung disease	5 (9%)
	- Coronary artery disease	15 (27%)
4.	Hemogram	
	- Haemoglobin (g/dL)	12.23±2.04
	- Neutrophils (10^9/L)	7.56±6.46
	- Lymphocytes (10^9/L)	1.02±0.49
	- Platelets (10^9/L)	232.33±87.74
	- Eosinophils (%)	0.45±0.82
5.	Day of illness on hospitalization (in days)	6.05±3.46
6.	Serum creatinine (mg/dL)	1.36±1.24
7.	Serum albumin (g/dL)	3.34±0.58

Categorical variable expressed as N (%), continuous variable expressed as mean and SD

Table 2 – Inflammatory markers among severe COVID-19 patients

S.no	Parameter	Mean ± SD	Median (IQR)
1.	NLR	10.17±12.32	6.68 (3.54–13.73)
2.	Serum Ferritin (ng/mL)	571.27±920.13	334.90 (173–667.50)
3.	LDH (U/L)	485.22±233.33	446 (348–530)
4.	D-dimer (mg/L FEU)	2.87±7.18	0.89 (0.50–1.50)
5.	CRP (mg/dL)	9.54±5.59	9.20 (6.0–13.20)
6.	SII	2577.93±3438.53	1439.17 (575.06–3802.05)
7.	FLPR	62.96±105.94	28.73 (12.79–62.02)

Note: NLR: neutrophil to lymphocyte ratio, LDH: lactate dehydrogenase, CRP: c-reactive protein, SII: systemic immune-inflammation index, FLPR: ferritin to lymphocyte percentage ratio

The median value of the SII was 1439.17, minimum calculated value was 182.80 and maximum value was 21495. FLPR mean value among severe category of COVID-19 patients was 62.96, median value was 28.73 and maximum value noted was 524.33 in our study. Mean ± SD of platelet to lymphocyte ratio (PLR) is 295.57± 208.89. Non-parametric Spearman correlation was assessed between novel biomarkers SII and FLPR with NLR and correlation is considered significant at the 0.01 level (2-tailed). SII index correlation with NLR for severe COVID-19 patients was statistically significant (p=0.0005) and correlation coefficient r value is 0.926 (Figure 1). FLPR correlation with NLR was found to be statistically significant among severe COVID-19 patients, p=0.0005 and correlation coefficient r value being 0.580 in our study (Figure 2).

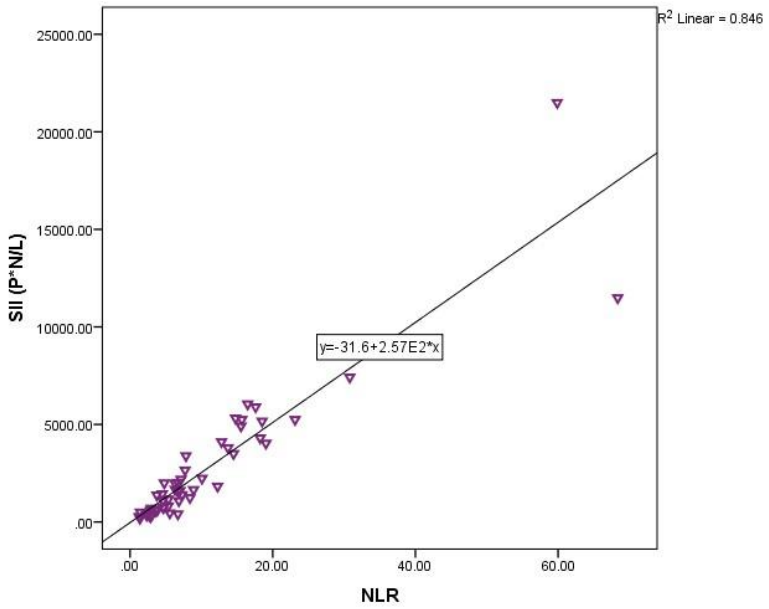

Figure 1 – Spearman correlation between SII index and NLR (r=0.926, p=0.0005)

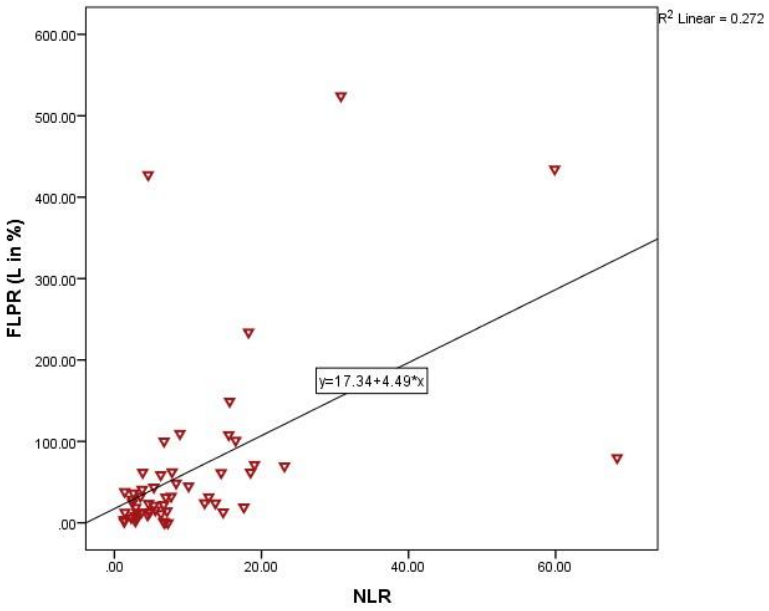

Figure 2 – Spearman correlation between FLPR and NLR (r=0.580, p=0.0005)

Raised serum creatinine (>1.3mg/dL) was seen in 22% of study patients (n=12) with mean serum creatinine of 1.36mg/dL. Hypoalbuminemia (<3.5g/dL) was seen in 64% (n=35) of severe COVID-19 patients, and seven patients had serum albumin less than 2.8g/dL, lowest observed value is 1.8g/dL. Of the total 55 patients, 26 recovered (47.3%) and 29 patients died (52.7%). Table 3 shows the various inflammatory biomarkers comparison between survivors and non-survivors of severe COVID-19 patients. Mann-Whitney test was used for association of biomarkers with outcome. We didn't find any statistical difference between survivors and non-survivors of severe COVID-19 with inflammatory biomarkers studied which include ferritin, LDH, CRP, D-dimer, SII index, FLPR. The descriptive data values of various biomarkers (mean, median value, and IQR) were many folds elevated despite being fairly similar among all severe COVID-19 patients, regardless of whether they survived or not. It should be noted that our study cohort was made up of only severe COVID-19 patients. This could account for the likely observed non-statistical significance.

Table 3 – Comparison of inflammatory markers between survivors and non-survivors of severe COVID-19

S.no	Parameter	Recovered (n=26)	Death (n=29)	P value
1.	Ferritin	413.05 (204.73–764.03)	313.10 (168–648.90)	0.292
2.	LDH	433.50 (346.50–518.20)	447 (333–622.50)	0.376
3.	CRP	9.20 (6.08–11.98)	9.20 (5–15.70)	0.572
4.	NLR	4.72 (2.45–10.56)	7.00 (4.65–14.12)	0.071
5.	FLPR	26.72 (8.72–77.58)	31.31 (15.09–61.90)	0.595
6.	SII	1125.26 (394.92–3070.80)	1668.56 (691.57–919.53)	0.138

Note: Variables expressed as median and IQR. LDH: lactate dehydrogenase, CRP: c-reactive protein, NLR: neutrophil to lymphocyte ratio, FLPR: ferritin to lymphocyte percentage ratio, SII: systemic immune-inflammation index

Dynamic changes in the values of the inflammatory markers were compared between admission and prior to the outcome studied (either at discharge or last value prior to death). To find the significant difference between the bivariate samples in paired groups, the Wilcoxon signed rank test was used and p value <0.05 was considered significant. We found a statistically significant difference between the mean values on admission and outcome for NLR (10.2±12.32 vs 21.9±21.3, p<0.0001), PLR (295.57±208.89 vs 539.9±804.9, p<0.01), SII (2577.93±3438.53 vs 4786±7624, p<0.001), FLPR (62.96±105.94 vs 219.8±612.7, p<0.003). The dynamic change in the inflammatory markers among severe COVID-19 patients had an increasing trend in this study. However, comparison of mean ferritin value between admission and discharge/death was statistically insignificant (571.3±920.13 vs 602±1014.5, p value-0.694). Figure 3 shows the mean values at admission and outcome (discharge or prior to death) for biomarkers studied which include NLR, PLR, SII, ferritin and FLPR.

DISCUSSION

In our study, patients aged >60 years and males (65%) were predominantly affected by severe COVID-19. Research has shown that, regardless of age, men were more likely to experience worse outcomes and severe COVID-19 disease [10, 11]. Men are possibly more vulnerable to COVID-19 because of the increased expression of the TMPRSS2 protein attributed to higher testosterone hormone levels [12]. Innate as well as adaptive immunity are vital for the control of viral infection. By interfering with type 1 interferons, SARS-CoV-2 impairs innate immunity [13]. An immune response which is dysregulated triggers hyperinflammation and cytokine storm, which in response induces an increase in inflammatory cells and/or chemokines such as TNF-α, IL-1, IL-6, and monocyte chemoattractant protein [14, 15]. The majority of severe patients had elevated proinflammatory and anti-inflammatory cytokines, such as IL-2, IL-6, TNF-α, and IL-10, which were significantly greater than those in mild cases, indicating that cytokine storms could be associated with the severity of the illness and outcomes [5].

SII is an inflammatory haematological marker which can be used in COVID-19 patients for diagnosis. In their study, Usul et al. proposed an upper limit of 479 for the SII to diagnose COVID-19 positive and negative patients [16]. The SII showed a significant correlation with NLR (r=0.926, p=0.0005) in our study's cohort of severe COVID-19 patients. The median SII value in survivors was 1125.26, while the median value seen among non-survivors was 1668.56 in our study. SII index cut off value > 618.8 predicted approximately 4.7-fold higher fatality and had a significant correlation with death, according to Karaaslan T et al. in their study of 191 COVID-19 patients [17]. With a total of 48 patients in the severe category, Xia W et al. looked at the SII index's ability to predict the severe COVID-19 earlier. They found that the SII, with a cut off value of 887.20, had an area under the curve (AUC) of 0.860 and a sensitivity and specificity of 81.25% and 81.82%, respectively, for predicting the early severe COVID-19 [18]. Ferritin plays a far more significant role in COVID-19 than being merely an acute phase reactant, since higher levels of ferritin have been associated to hyperinflammation and or cytokine storm, disease severity and fatality. Any kind of insult or injury results in secretion of inflammatory cytokines which acts on liver and in turn, liver produces various defence proteins like CRP, ferritin. Inflammatory mediators in COVID-19 like interleukins (IL-1β, IL-6) and IFN-γ induces transcription and translation of gene coding for ferritin. Recruited inflammatory cells and macrophage causes further increase in ferritin levels. Ferritin acts as a pro-inflammatory mediator, boosting further inflammatory responses and establishing a vicious cycle via nuclear factor-κB (NFκB) activation. NFκB plays a pivotal role in inflammatory genes expression and promotes transcription of ferritin gene [19, 20].

Hyperferritinemic syndrome characterised by higher ferritin levels (usually >1000ng/ml) is seen in macrophage activation syndrome, systemic juvenile idiopathic arthritis (sJIA), adult-onset Still's disease, antiphospholipid antibody syndrome [21]. Severe COVID-19 also causes hyperferritinemic state. Studies have shown significant association between higher ferritin levels and death among COVID-19 patients. Wu C et al. in their study conducted among the group with acute respiratory distress syndrome (ARDS) secondary to COVID-19, elevated ferritin levels between survivors and dead were found to be insignificant [22]. Similarly in our study, the mean serum ferritin value (603.14±1213.38 ng/mL) of non-survivors did not differ significantly from that of survivors (535.71±421.06 ng/mL) of severe COVID-19.

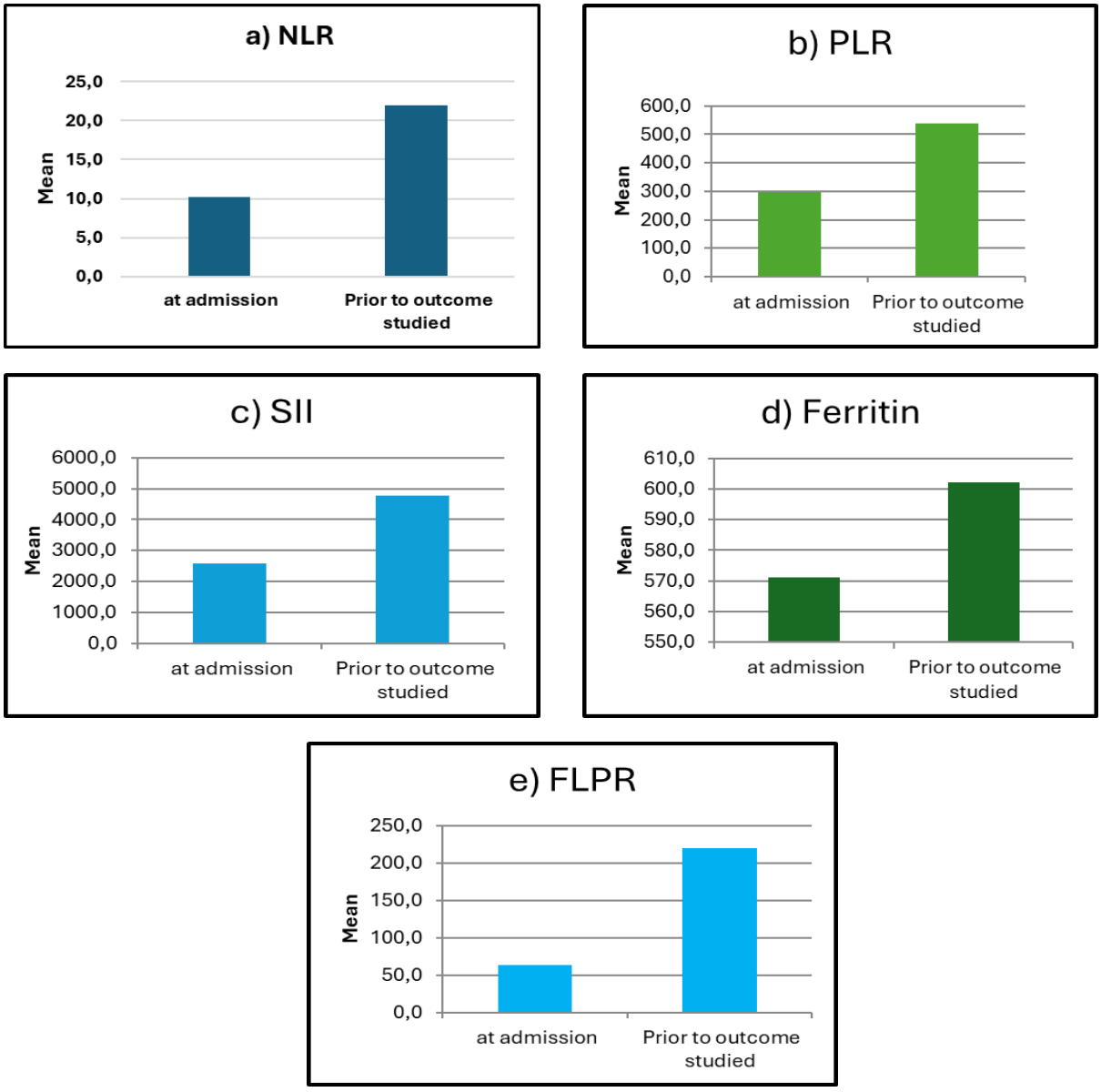

Figure 3 – Graphical representation of mean values of a) NLR, b) PLR, c) SII, d) Ferritin, e) FLPR at admission and outcome (discharge or prior to death). NLR-Neutrophil to lymphocyte ratio; PLR-Platelet to lymphocyte ratio; SII-systemic immune inflammation index; FLPR-Ferritin to lymphocyte percentage ratio

Auygun H et al. investigated whether FLPR could be used to predict mortality in their study of 331 COVID-19 patients and noted that groups with critical [median (IQR), 84.62 (39.76–148.60)] and severe COVID-19 [median (IQR), 27.32 (14.18–59.03)] had higher FLPR levels [23]. The area under the curve (AUC) value was found to be 0.909 (95% confidence interval [CI]: 0.857–0.961) in the ROC analysis. The sensitivity and specificity of the FLPR cut-off value of 9.80 were found to be 96.7 percent and 65.2 percent, respectively, for

predicting the likelihood of death whereas the sensitivity and specificity for mortality prediction were reported to be 82.9% and 82.8%, respectively, when the FLPR cut off value was 21.11 [23]. Similarly in our study, median (IQR) value of FLPR observed among the severe COVID-19 patients (n=55) was 28.73 (12.79-62.02). Non-survivors (n=29) in our study had a higher median (IQR) FLPR value of 31.31 (15.09-61.90). Auygun H et al. in their study observed mortality rate of 12.4% (41 deaths out of 331 patients) and the non-survivor group had a much higher median (IQR) FLPR value of 83.15 (31.67–184.08) compared to our study group [23]. A retrospective study done by Yurt NS et al. among 309 COVID-19 patients including 118 severe/critical COVID-19 showed FLPR on admission can be used to predict 30-day mortality and it had higher predictive power than other biomarkers like CRP, ferritin, neutrophil count, lymphopenia [24]. They also observed significantly higher mean value of FLPR among non-survivors (175.65±205.19) and a cut off value of 42.4 predicted mortality with a sensitivity of 84% and specificity of 87%. Various studies assessing the inflammatory biomarkers (FLPR, SII, ferritin) in COVID-19 is shown in Table 4. In our study, we found significant correlation between FLPR and NLR (r=0.580, p=0.0005). Yurt NS et al. found a moderately positive correlation of FLPR with radiological severity assessed by computerised tomography scores (r=0.496, p<0.001) [24].

Table 4 – Findings of studies assessing inflammatory markers like FLPR, SII, ferritin among COVID-19 patients

S.no	Authors	Study design	Sample size	Findings
1.	Aygun H et al. [23]	Retrospective study during first wave of COVID-19 (April 2020)	n=331, (included mild, moderate, severe and critical COVID-19)	FLPR was significantly associated with disease severity (p<0.05). FLPR cut off value of 21.11 predicts mortality with sensitivity of 82.9% and specificity of 82.8%
2.	Nur Simsek Yurt et al. [24]	Retrospective cohort study (February 2021 to march 2021)	n=309, included mild, moderate, severe and critical COVID-19)	The cut-off value of FLPR found to predicting 30-day mortality was 42.4. (sensitivity-84.2% specificity-86.7%, area under the curve-0.924)
3.	Usul, Eren et al [16]	Retrospective study (March 2020 to April 2020)	n=289 with suspected COVID-19	NLR, SII can be used to diagnose COVID-19. Significant difference in NLR, SII was found between test negative and test positive group (p<0.05)
4.	Wu C, Chen X et al. [22]	Retrospective cohort study (December 2019-January 2020)	201 patients with COVID-19 pneumonia	Serum ferritin value had no statistically significant difference between survivor's vs non-survivors among the ARDS group (853 ng/ml vs 1096 ng/ml, p value=0.34)
5.	Karaaslan T, Karaaslan E et al. [17]	Retrospective study design, conducted in two centres	191 patients with all categories of COVID-19	SII had a positive correlation with NLR (r-0.812, p <0.001) and mortality (p <0.001). SII value more than 618 had a five times higher mortality risk
6.	Xia W, Tan Y, Hu S et al. [18]	Retrospective study (January 2020 to march 2020)	125 patients (Severe cases, n=48)	NLR value of 7.25 and SII value of 887 predict severity earlier among patients with COVID-19

Note: SII-systemic immune inflammation index; NLR-Neutrophil to lymphocyte ratio; PLR-Platelet to lymphocyte ratio; FLPR-Ferritin to lymphocyte percentage ratio; ARDS-acute respiratory distress syndrome

Interleukins and tumour necrosis factor alpha secreted during inflammatory response causes lysis of lymphocytes expressing ACE. This results in lymphopenia. Decrease in lymphocyte % has a significant correlation with length of stay and portends poor outcomes among COVID-19 patients. Lymphopenia was observed among 96% of critically severe COVID-19 patients by Guan WJ et al [25]. Ferritin, an intracellular protein is the storage form of iron existing in two subunits namely, ferritin light chain and ferritin heavy chain. Ferritin heavy chain subunit increases during inflammatory states and causes

immune dysregulation. Ferritin facilitates inflammatory response by activating macrophages as well produces immune suppression, thereby setting cytokine storm. It is the inflammatory mechanism which has an integral role in multiorgan dysfunction and death in SARS-CoV-2 infection. It seems decrease in lymphocyte percentage and increase in serum ferritin levels appears to be related to the destruction of hematopoietic cells by COVID-19 infection [23,24]. Inflammatory biomarkers combining elevated ferritin and lower lymphocyte percentage could serve as a prognostic marker in COVID-19. Hence FLPR used early in the course of COVID-19 has the potential for prognosticating the disease outcome.

CONCLUSIONS

We found a significant positive correlation between SII and NLR. Novel inflammatory biomarker FLPR showed a positive correlation with NLR in our cohort which comprised of patients with severe COVID-19. Hence its sensible to make use of SII and FLPR in COVID-19 patients for assessing the severity of illness and prognosticating the disease. Along with NLR, SII and FLPR serves as a robust inflammatory biomarker in risk stratifying the disease and predicting the outcome. Ferritin, LDH, NLR, D-dimer, CRP, and SII were among the inflammatory biomarkers with higher values among the severe COVID-19 patients in our study.

Limitations of our study: Our study design was retrospective which was conducted during first wave of COVID-19 pandemic in a single centre designated for COVID-19 treatment. Our sample size was small. We did not compare the SII, FLPR and other inflammatory biomarkers between mild/moderate disease with severe COVID-19. Being a single centre study with smaller sample size, generalization or representative of the findings to other regions is limited and warrants multicentric study with larger sample size. Only severe COVID-19 was included in this study which might explain the statistical insignificance of novel markers, hence comparison of markers across all categories of COVID-19 might be clinically useful in predicting the outcomes. It is to be noted that many variants of COVID-19 have emerged since the first wave, and our study done during first wave may not be replicative of subsequent COVID-19 variants.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Novel inflammatory biomarkers like FLPR, SII needs to be studied prospectively with larger sample size in patients with emerging COVID-19 variants in prognosticating disease severity and hospitalisation outcome. FLPR can be used as a tool to stratify patients as mild, moderate, severe, critical COVID-19. The cut-off value predicting the disease stratification is an area of future research in COVID-19.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

VP, AK, SG - conception and design feasibility assessment
VP, LM, SM, VR - acquisition of data, analysis and interpretation
VP, AK, LM, SG, SM, VR - literature search, drafting of manuscript
VP, AK, LM, SG, SM, VR - supervision, critical review and final approval of manuscript and guarantor

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None.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

USE OF ARTIFICIAL INTELLIGENCE (AI) / ВИКОРИСТАННЯ ШТУЧНОГО ІНТЕЛЕКТУ

The authors did not use AI in this paper.

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