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Hematological parameters in COVID-19 patients at admission in a tertiary care centre in central India

Kavita Jain[1], Dhananjay Naik[2], Dharampal Chouhan[3], Shirish Nandedkar[4], Manju Purohit[5]

[1]Associate Professor, Department of Pathology, R D Gardi Medical college, Ujjain- Madhya Pradesh, India
[2]Assistant Professor, Department of Pathology, R D Gardi Medical college, Ujjain- Madhya Pradesh, India
[3]Assistant Professor,Bio- statistics, R D Gardi Medical college, Ujjain, Madhya Pradesh, India
[4]Professor, Department of Pathology, R D Gardi Medical college, Ujjain, Madhya Pradesh, India
[5]Professor and Head of Department of Pathology, R D Gardi Medical college, Ujjain, Madhya Pradesh, India

Abstract

Introduction: Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 virus is an acute respiratory infection with systemic manifestations.Studies have shown that abnormal hematological parameters can help in prognostication of patients. Our study analyses hematological parameters for prognostication and prediction of mortality in SARS-CoV-2 patients from central India. **Aim:** Present study aims to compare the mean value of hematological parameters from 350 hospitalized COVID-19 patients (survivors and non-survivors), in order to assess their role in prognostication and prediction of mortality. Our study evaluates complete blood count (CBC) and their ratios, neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR) and systemic immune inflammation index (SII) in COVID-19 patients admitted to a tertiary care hospital in central India. **Materials and Methods:** Retrospective cross-sectional study was performed on 350 patients hospitalized for treatment of COVID-19. They were divided into two groups on the basis of their outcome: group 1 comprised of 28 non- survivors; group 2 comprised of 322 survivors.**Results:** Male predominance was seen in both survivors and non survivors.Mortality rate was 8%. Statistically significant differences were observed with respect to total leucocyte count (TLC), neutrophil percent (N%), absolute neutrophil count (ANC), Lymphocyte percent (L%), zero eosinophil percent (E%), absolute eosinophil count (AEC), NLR, MLR, PLR and SII at admission between survivors and non survivors of COVID-19 patients.**Conclusion:** Elevated TLC, neutrophil percent, ANC, NLR, MLR, PLR and SII at admission are useful in prognostication and prediction of mortality in COVID-19 patients.
Keywords: Hematology parameters, COVID-19, NLR, SII, neutrophil count, eosinophil.

Introduction

First reports of outbreak of cases of pneumonia in December 2019 came from Wuhan (People's Republic of China) [1]. The causative agent is a novel Corona virus, named as severe acute respiratory syndrome Corona virus 2 (SARS –CoV-2). Infection caused by this virus was termed Corona virus disease- 2019 (COVID-19) [2]. With global spread of this infection, World Health Organization (WHO) declared it as a pandemic on 11th March 2020[3].As of 30th June 2021, there have been 3,03,16,897 confirmed COVID-19 cases and 3,97,637 deaths related to it in India [4].

Significant findings in routine hematological parameters have been reported from western population and Asian countries including India [5-14]. Present study was undertaken due to paucity of data on hematological parameters from central India.

Aim and objective
Aim of this study was to correlate mean value of hematological parameters i.e. mean hemoglobin (Hb), mean red cell distribution width- standard deviation (RDW-SD), mean total leucocyte count (TLC), mean neutrophil percent (N%), mean absolute neutrophil count (ANC), mean lymphocyte percent (L%), mean absolute lymphocyte count (ALC), mean eosinophil percent (E%), mean

*Correspondence
Dr.Kavita Jain
Associate Professor Pathology, Department of Pathology, R D Gardi Medical college, Ujjain, Madhya Pradesh, India
E-mail: kjain1974@rediffmail.com

absolute eosinophil count (AEC), mean platelet count and their ratios (neutrophil lymphocyte ratio-NLR, monocyte lymphocyte ratio-MLR, platelet lymphocyte ratio- PLR as well as systemic immune inflammation index -SII) on admission in survivors and non survivors of 350 hospitalized COVID-19 patients at a tertiary care hospital in central India. The objective was to find out the cut off values of different hematological parameters for prediction of mortality in COVID-19 patients.

Materials and methods
Study Design: Retrospective cross-sectional study.
Participant's inclusion and exclusion criteria:350 real time reverse transcription polymerase chain reaction (RTPCR) positive COVID-19 hospitalized patients of age more than 12 years and of both genders were included in the study.
Exclusion criteria for the study were:
a)   Patients who were admitted for COVID-19 treatment but were of age 12 years or below.
b)   RTPCR positive cases who got referred elsewhere within 24 hours of admission
c)   As well as SARS-CoV-2 RTPCR negative cases.
Place and duration of study:A single institution based retrospective cross-sectional study in a COVID-19 dedicated tertiary care centre attached to medical college in central India, from mid May 2020 to mid September2020. This study was approved by ethical committee of the institute.

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Methodology for sample collection and reporting: Universal precautions and WHO guidelines for sample collection of COVID-19 cases was followed [15]. For SARS-COV-2 RTPCR, nasopharyngeal/ oropharyngeal swabs were collected by trained paramedical staff and RTPCR was carried out in molecular laboratory department of the institute. Whole blood samples of the studied population (350 patients) were collected for analysis in Ethylene-di-amine tetra-acetic acid (EDTA) vacutainers by trained nursing staff/ paramedical staff and were analyzed on SYSMEX XN- 550L six-part hematology analyzer in pathology department of the hospital.

Data Collection: Demographic data, hematology parameters of these patients on admission as well as their final outcome were extracted from the Hospital management and Laboratory information system. The data collected was then transferred to Microsoft excel sheet. NLR, MLR, PLR and SII was calculated and entered in the data sheet. NLR was calculated by dividing absolute neutrophil count by absolute lymphocyte count. Similarly, MLR was obtained by dividing absolute monocyte count by absolute lymphocyte count. PLR was also achieved by dividing platelet count by absolute lymphocyte count. SII was calculated as= (absolute neutrophil count x platelet count)/absolute lymphocyte count.

On the basis of the disease outcome, these 350 patients were then divided into two principal groups, group 1, and group 2. Group 1 had 28 non survivors of the total 350 patients and group 2 had the rest 322 survivors of COVID-19 infection.

Statistical analysis

SPSS 21.0 version statistical software was used for analysis. Continuous variables were presented as mean ± standard deviation (SD). Categorical variables were expressed as frequencies and percentages. Chi square test was used to calculate difference between qualitative variables. t-test was used to measure differences in means of different parameters. p-value less than 0.05 was considered as statistically significant. Receiver-operating characteristic (ROC) curve for sensitivity, specificity values was analyzed for predicting mortality among groups.

Results

Demographic data: The mean age of patients in RTPCR positive COVID-19 cases was 53 years. Most patients were in 4th-6th decade, followed by those in 7th decade and more. Mortality was comparatively higher in patients with age more than 60 years with statistically significant p value of 0.006 (Table 1). Male predominance was seen with 232 males of 350 COVID-19 patients, and this was also observed in both the groups (non survivors and survivors).

Hematological parameters: Table 1 gives hematological parameters (mean values ± SD) observed in non survivors and survivors of 350 COVID-19 patients and correlation between them (p value). Normal range of hemoglobin (Hb), total leucocyte count (TLC), neutrophil percent (N%), absolute neutrophil count (ANC), lymphocyte percent (L%), absolute lymphocyte count (ALC), eosinophil percent (E%), absolute eosinophil count (AEC) and platelet count as per our laboratory cut offs are also shown in footnotes of table1.

Table 1: Comparison of mean values of hematological parameters according to outcome (non survivors and survivors) in COVID -19 patients

Variables	All cases (N=350)	Non survivors, Group 1 (n=28)	Survivors, Group 2 (n=322)	p- value
Demographic Parameters				
Age (years)				
>12-30	45	0	45	
31-60	181	11	170	0.006
> 60	124	17	107	
Gender				
Males	232	17	215	
Females	118	11	107	0.516
Male: Female	1.96:1	1.54:1	2.00:1	
Hematological Parameters[*]				
Hemoglobin[†]	12.90 ± 2.51	12.51 ± 2.91	12.93 ± 2.07	0.326
RDW – SD[‡]	43.98 ± 6.75	45.03 ±7.95	43.89 ± 6.65	0.392
TLC[§]	8633 ± 5871	11831 ± 7561	8355 ± 5630	0.003
Neutrophil percent[ǀ]	71.77 ± 16.43	85.81 ±7.55	70.55 ±16.43	0.000
ANC[¶]	6575 ± 4887	10977 ± 7316	6192 ±4431	0.000
Lymphocyte percent[**]	21.78 ± 15.06	9.34 ± 6.02	22.86 ± 15.13	0.000
ALC[††]	1659 ± 3382	1282 ± 1794	1692 ± 3486	0.539
Eosinophil percent[‡‡]	0.60 ± 1.21	0.05 ± 0.17	0.64 ± 1.25	0.012
AEC[§§]	38.50 ± 82.36	3.79 ±10.81	41.52 ± 85.15	0.020
Platelet count[ǀǀ]	2.42 ± 0.95	2.68 ± 1.26	2.40 ± 0. 92	0.128
NLR	7.21 ± 8.41	15.03 ± 13.00	6.53 ± 7.54	0.000
MLR	0.34 ± 0.34	0.51 ±0.44	0.32 ± 0.33	0.005
PLR	242.86 ± 229.89	412.50 ± 463.06	228.11 ± 191.56	0.000
SII	1831.784 ± 2442.506	3978.772 ± 3660.671	1645.090 ± 2218.565	0.000

[*]Data are presented as mean ± standard deviation (SD)

Reference range-[†]hemoglobin:12-16 g/dl; [‡]red cell distribution width-standard deviation: 35-56 fl, [§]total leucocyte count: 4000- 11000 cells /µL, [ǀ]neutrophil percent: 50%- 70%, [¶]absolute neutrophil count: 2000- 7000 cells/µL,[**] lymphocytepercent: 20%- 40%, [††]absolute lymphocyte count: 800-4000 cells/µL, [‡‡]eosinophil percent: 0%- 6%· [§§]absolute eosinophil count: 20- 450 cells/ µL·[ǀǀ]plateletcount: 1.5- 4.5 lac/ µL.

Abbreviations: NLR: neutrophil to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, PLR: platelet to lymphocyte ratio, SII: systemic immune inflammation index

Comparison of hematological parameters

Mortality rate of 8% was observed in the 350 RTPCR positive COVID-19 cases as it included 28 non survivors (group1) and 322 survivors (group 2). In the global cohort of 350 COVID-19 cases, 9.42% cases had leucopenia, 21.7% had leucocytosis and 23.7% had

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lymphopenia. 9.62% of non survivors and 7.14% of survivors had leucopenia. Leucocytosis was seen in 42.8% of non survivors and in 19.8% of survivors. 42.85% of non survivors and 22.05% of survivors had lymphopenia.

Statistically significant differences (*p* value < 0.05) were observed with respect to mean values of TLC, neutrophil percent, absolute neutrophil count, lymphocyte percent, eosinophil percent, absolute eosinophil count, NLR**,** MLR, PLR and SII at admission between the non survivors and survivors (table 1).

ROC curve analysis of hematological parameters

We analyzed cut off values calculated by ROC analyses and the ROC curves are presented in figure1. We chose the variables with more than 0.6 area under receiver operating characteristic curve. Thus, TLC, neutrophil percent, ANC, NLR, MLR, PLR and SII were found

to have AUC of 0.654 (*p*=0.007), 0.785 (*p*=0.000), 0.717 (*p* =0.000), 0.783 (*p*=0.000), 0.659 (*p*=0.000), 0.681 (*p*=0.000) and 0.737 (*p*=0.000) respectively, as shown in table 2.

On ROC curve analysis (figure 1), taking sensitivity and specificity into consideration, the cut off values for significant hematological parameters were, TLC ≥ 8115 cells/µL, neutrophil percent ≥ 84.25%, ANC ≥ 7131.98 cells/µL, NLR ≥ 8.57, MLR ≥ 0.27, PLR ≥ 231.75 and SII ≥ 2050.076 for prediction of mortality in COVID-19 patients (table 2).
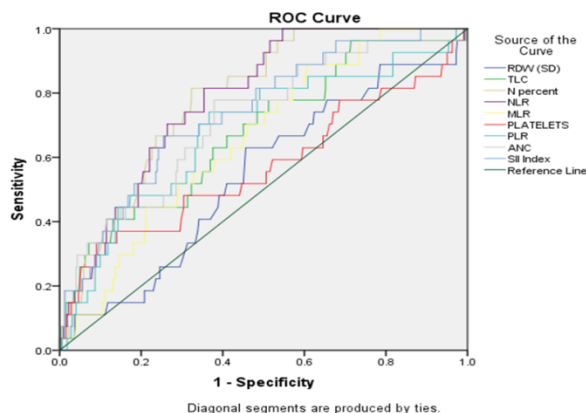

Fig 1: Receiver operating characteristic (ROC) curve for significant markers in the COVID-19 patients

Table 2: ROC curve analysis for SARS-CoV-2 patients (N=350)

Markers	AUC	Cut off	Sensitivity	Specificity	95% CI	*p* value
TLC[*]	0.654	≥ 8115.00	60%	62%	0.542-0.767	0.007
Neutrophil percent[†]	0.785	≥ 84.25	70%	72%	0.714-0.855	0.000
ANC[‡]	0.717	≥ 7131.98	63%	69%	0.616- 0.819	0.000
NLR	0.783	≥ 8.57	70%	73%	0.713- 0.853	0.000
MLR	0.659	≥ 0.27	63%	58%	0.566-0.751	0.000
PLR	0.681	≥ 231.75	70%	65%	0.57- 0.792	0.000
SII	0.737	≥ 2050.076	63%	75%	0.643-0.831	0.000

Reference range: [*]total leucocyte count: 4000- 11000 cells /µL, [†]neutrophil percent: 50%- 70%, [‡]absolute neutrophil count: 2000-7000 cells/µL

Abbreviation: ROC: receiver operating characteristic, AUC: area under curve, CI: confidence interval, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index

Discussion

Present study of 350 admitted COVID-19 patients (232 males and 118 females) shows that hematological parameters and their ratios at admission are effective tools for prognostication and prediction of mortality.

Several studies have been published with regards to importance of epidemiological, clinical, radiological and laboratory data in COVID-19 patients [5-14]. Most of these studies have in general shown that COVID-19 illness was more predominantly seen in males and in age group of more than 40 years [5-8, 10-14].

In present study too, male preponderance was seen in both the groups (non survivors and survivors). Most of these patients belonged to 4th to 6th decade of life. Mean age of patients was 53.0 which is comparable to the findings in epidemiological data shown in literature till now. 60.7% patients who succumbed to illness were of

60 years and above which might have been as a result of presence of comorbidities in them. COVID-19 cases in our study showed predominantly leucocytosis with neutrophilia and low lymphocyte percent. Consequently, they had increased NLR, MLR and PLR. According to studies till date, raised NLR constitutes the most significant hematological alteration in COVID-19 cases and NLR, neutrophilia, lymphopenia, and leucocytosis correlate with disease severity [8-14].

Usually, bacterial infection causes severe neutrophilia and viral infection causes lymphocytosis, so NLR was used to distinguish between these two types of infections. To the contrary, COVID-19 cases showed moderate to severe neutrophilia with lymphopenia and thus higher NLR than healthy population. Absolute neutrophil count (ANC) was also observed to be significantly higher in group 1 (non survivors). This neutrophilic response seen is due to virus related inflammatory factors produced by lymphocytes and endothelial cells [6, 8]. Lymphopenia could be attributed to several mechanisms including the effects of direct viral infection, as well as the result of immune response and metabolic disorders seen in these patients [16]. One of the most important reasons being that the SARS-CoV-2 virus attaches to angiotensin.converting enzyme 2 receptors (ACE2) on the surface of lymphocytes via its spike proteins and thus infects and

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lyses them. In addition, the cytokine storm as a result of raised levels of interleukins (like IL-6, IL-2, IL-7, granulocyte colony stimulating factor, interferon gamma inducible protein 10, MCP-1, MIP1-a) and tumour necrosis factor- alpha (TNF-α) promotes lymphocyte apoptosis [17-20]. Fan et al found prominent lymphopenia in ICU patients [10]. In our present study, we too observed that lymphocyte percent was lower in COVID-19 patients and severely low in patients with poor outcome (mean lymphocyte percent was 9.34% in non survivors i.e., group 1).NLR has been studied earlier as a prognostic marker in acute respiratory distress syndrome [21]. NalbantAhmet concluded from his study that NLR is significantly elevated in COVID-19 patients and observed that cut off value of NLR of ≥2.4 increases the likelihood of COVID-19 infection by 20.5 times [22]. Similarly, other studies have observed that elevated NLR was an independent prognostic marker in COVID-19 patients [8, 23]. In our study, we too observed a higher mean NLR value of 7.21 in COVID-19 patients. Patients within group1 (fatal cases) had a significantly (*p* value <0.005) higher mean NLR value of 15.03 versus 6.53 in group 2 (patients who got successfully treated). A cut off value of NLR of ≥ 8.57 (sensitivity 70% and specificity 73%) on admission in patients with COVID-19 symptoms was calculated from AUC of ROC curve for the admitted 350 patients which would help to predict mortality (table 2).

Monocyte to lymphocyte ratio (MLR) has been observed to be higher in COVID-19 cases and is predominantly due to lymphopenia, as explained earlier and also as a result of mobilization of lymphocytes from peripheral blood into pulmonary tissue. AliyeBastug et al got a cut off value of ≥ 0.31 for MLR to diagnose critically ill COVID-19 patients on admission [24]. Peng et al concluded from their study of 190 COVID-19 patients versus healthy subjects that monocyte to lymphocyte ratio (MLR) has high diagnostic value in differentiating COVID-19 cases from healthy individuals with optimal cut off value of 0.23 (sensitivity 75.79% and specificity of 90%) [25]. Study on hospitalized chronic kidney disease patients with COVID-19 infection by Ramses et al confirmed that higher MLR in these patients carries higher mortality. Importantly, in our study we too confirmed that MLR at admission was higher with a cut off of ≥ 0.27 in predicting mortality [26].

Normal to mild thrombocytopenia has been observed in few studies on COVID-19. In some studies, platelet count was found to be significantly reduced in severe cases [18]. This might be due to sepsis induced disseminated intravascular coagulopathy and/ or direct platelet- viral interaction [27]. Even though platelet count was not statistically significant between fatal (group 1) and non-fatal positive cases (group 2), the PLR was significantly higher in group 1 and had a cut off value of 231.75 (sensitivity 70% and specificity of 65%) for prediction of mortality in RTPCR positive COVID-19 patients. A study by RongQu highlighted that increase in PLR during treatment was associated with longer hospital stay. Their study recommended prompt intervention to prevent further deterioration when the PLR is > 126.7 [28]. In our study, we found that role of platelet count as an independent prognostic biomarker could be limited due to thrombocytopenia seen in association with other pneumonias, malaria, and dengue in our region. So, both MLR and PLR will serve as a useful prognostic marker in hospitalized cases as shown in our study and others

The other hematological parameters of statistical significance were percentage of eosinophils in the differential count and absolute eosinophil count (AEC) at admission of COVID-19 cases. Eosinophils are increased in CBC in patients with parasitic infections and allergies. Role of eosinophils in peripheral blood has been analyzed in few studies on COVID-19 patients including fatal cases and all of them have documented severe eosinopenia at admission and its role as indicator of poor outcome [29-33]. It has been stated in these studies that cause of this eosinopenia can be multifactorial, as a result of decreased eosinophil synthesis in bone marrow to increased eosinophil apoptosis due to type 1 interferons. In fact, we had zero

percent eosinophils in 47% of COVID-19 cases in our study. Like in earlier studies, our data also showed severe eosinopenia on admission with zero eosinophils in 82% of fatal cases. Thus, eosinopenia on admission can be useful indicator of poor outcome in patients with COVID-19. Systemic immune inflammation index- SII; calculated as product of neutrophil count and platelet count divided by lymphocyte count {(neutrophils x Platelets)/lymphocytes} has been seen to correlate with severity of illness and mortality in SARS-CoV-2 infection. Role of elevated SII as a novel prognostic indicator in predicting in- hospital mortality was observed in some studies [34, 35].Alessandro et al got an optimized cut off value of SII of 1835 in their study for prediction of survival. In present study, we also observed a cut off value of more than 2050.076 (sensitivity 63% and specificity of 75%) for prediction of mortality by analysis of ROC curve between the two groups.

Conclusion
1. Hematological parameters i.e., elevated TLC, neutrophil percentage, ANC, NLR, MLR, PLR and SII will be helpful for prognostication in COVID-19 cases at admission.
2. Cut off value for TLC ≥ 8115 cells/ µL, neutrophil percent ≥ 84.25%, ANC ≥ 7131.98 cells/ µL, NLR ≥ 8.57, MLR ≥ 0.27, PLR ≥ 231.75 and SII ≥ 2050.076 help in prediction of mortality in COVID-19 cases.

Limitations and further perspective
Our study had few limitations as we could not obtain sufficient clinical history for analysis, and we only analyzed hematological parameters on admission. We also recommend further studies in central India for comparison of hematological parameters in hospitalized RTPCR positive cases versus patients who were suspected with SARS-CoV-2 infection but were RTPCR negative.

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