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Prognostic Significance of Hematological Parameters and Ratios in COVID-19 Patients

Anjali Sharma[1], Mukul Singh[1], Manju Kumari[1*], Heena[2] Gopal Chand[1], Sunil Ranga and Jugal Kishore[2]

[1]Department of Pathology, VMMC and Safdarjung Hospital, New Delhi, India

[2]Department of Community Medicine, VMMC and Safdarjung Hospital, New Delhi, India

Corresponding e-mail: manju.yadav126@gmail.com

ABSTRACT

Background and aim: *Coronavirus Disease 2019 (COVID-19) is caused by the virus SARS-CoV-2 and has affected millions of individuals across the world. Various haematological parameters and prognostic factors have been studied in the Chinese population. We here aimed to evaluate these haematological parameters in the Indian population and to search for any early prognostic factors of severe illness.* ***Material and methods:*** *The haematological parameters were assessed in 829 COVID-19 positive patients. The trend of these parameters was studied in the hospitalized patients and these parameters were also compared between survived and expired patients with a two-tailed pair t-test in the SPSS software version.* ***Results:*** *Out of 829, 504 (60.79%) were males and 325 (42.46%) were females. Among these 67 (8.1%) expired. All the haematological parameters were within the normal range but when their trend was studied in repeated samples of hospitalized patients we found that there was a significant difference in platelet count (p=0.000), eosinophil count (p=0.020), and platelet to lymphocyte ratio (p=0.004). Also, the difference of WBC (p=0.000), lymphocyte count (p=0.001), neutrophil count (p=0.001) and NLR (p=0.006) was significant between survived and non-survived patients. The patients who died had higher WBC count (mean=9996/µl) and lymphopenia (25.19%) in comparison to those who survived (mean WBC=7656/µl and Lymphocyte=30.34%). They also had higher neutrophil count and NLR than survived patients.* ***Conclusion:*** *The parameters like WBC count, lymphocyte count, neutrophil count, and NLR are significantly higher in non-survived in COVID 19 positive patients. These parameters can serve as biomarkers in predicting the prognosis and severity of the diseased.*

Keywords: COVID 19, Coronavirus, Hematological parameters, Platelet count, Platelet to lymphocyte ratio, Neutrophil to lymphocyte ratio

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is caused by the novel virus Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which is now a rapidly evolving pandemic involving millions of individuals all over the world. It was named SARSCoV-2 due to 79% homology with SARS-CoV [1]. Initially, it was believed that this virus affects mainly the respiratory system but current emerging data indicates that it is a systemic disease involving respiratory, cardiovascular, gastrointestinal, neurological, hematopoietic, and immune systems [2-4]. COVID-19 is more lethal than the seasonal flu however, it has a lower mortality rate than previous coronavirus respiratory infections like Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) [5]. Most of the patients have mild to moderate symptoms and they recover after symptomatic treatment with medical interventions in some of them. However, 15%-32% of patients develop severe disease with a mortality rate of 1%-15% [6]. Individuals with comorbidities and higher age have an increased risk of mortality however young individuals without any comorbidity can also present with severe myocarditis, Disseminated Intravascular Coagulation (DIC), and multiple organ failure [7].

In recently published literature it is mentioned that COVID-19 is prone to cause haematological changes with some differences in severe and non-severe cases. Most of these studies were done in the Chinese population. Still, there is

very scarce information about various haematological parameters and ratios in COVID-19 patients. Here, we have studied various haematological parameters and ratios in the Indian population.

MATERIAL AND METHODS

This is a retrospective study carried out in the department of emergency (Pathology) from March 2020 to May 2020. 829 COVID-19 positive patients were included in the study. Of these repeated samples were received for 225 patients and 67 expired. We collected 2 ml of blood in an EDTA vacutainer. The haematological parameters were obtained from automated hematoanalyzer (White Blood Cell count (WBC), Absolute Neutrophil Count (ANC), Absolute Lymphocyte Count (ALC), Absolute Monocyte Count (AMC), Platelet Count (PC), Mean Platelet Volume (MPV)) were studied. Along with these haematological ratios like Neutrophil to Lymphocyte Ratio (NLR), Monocyte to Lymphocyte Ratio (MLR), Platelet to Monocyte Ratio (PMR), and Platelet Count to Mean Platelet Volume Ratio (PC/MPV ratio) was calculated. Any deviation from the normal values was noted. Following was the reference range of various haematological parameters included in the study [8].

White blood cell: (4000-10000)/µl, absolute neutrophil count: (2000-7000)/µl,absolute lymphocyte count: (1000-3000)/µl, absolute monocyte count: (200-1000)/µl, platelet count (150,000-400,000)/µl MPV: 7.5-12 fl, NLR: 2-2.33, MLR: 0.2-0.33, PLR: 136.67-150, Platelet: MPV: 20-34.17

The trend of all of the above parameters was noted in samples received repeatedly of the same patients. The individuals were divided into two groups: survived and non-survived. The above parameters were also compared in these two groups. The statistical analysis was done by SPSS software version. A two-tailed paired t-test was applied. A p-value of less than 0.025 was considered significant.

RESULTS

A total of 829 patients were included in the study of which 504 (60.79%) were males and 325 (42.46%) were females. Only 18 (2.17%) of these were of pediatric age groups (<15 years). Age-wise distribution of the survived and non-survived patients is shown in Table 1. Among these 829 patients, 67 (8.1%) patients expired whereas the rest were discharged after recovery. The mortality rate was higher in males (68.66%) than females (31.34%). The haematological parameters of all the patients (one-time sample as well as repetition sample) were analyzed and are tabulated in Table 2. All these parameters were within the normal range. We further compared these parameters in samples that were received more than one time and studied the trend of these parameters. Of all the parameters the significant difference was noted in platelet count (p=0.000), eosinophil count (p=0.020), and platelet to lymphocyte ratio (p=0.004) (Table 3). Initially, these patients had thrombocytopenia and low eosinophil count which was increased on recovery.

Table 1 Age-wise distribution of survived and expired patients

Age Group	Survived	Expired
<15 years	18	0
16-30 years	127	10
31-50 years	465	30
51-70 years	173	16
71-90 years	46	11
Total	829	67

Table 2 Mean of the haematological parameters in COVID19 positive patients and the number of patients having low and high values of these parameters

Parameter	Mean	Percentage of individuals with low value	Percentage of individuals with high value
WBC count	7.67×10^3/µl	8.23	19.15
PC	195.39×10^3/µl	40.1	6.43

ALC	2326/µl	8.45	11.44
ANC	4596/µl	13.05	16.25
AMC	462 µl	18.61	6.42
NLR	1.98	51.41	37.72
MLR	0.19	55.35	19.29
PLR	6.44	100	0
PC/MPV	19.08	59.63	12.55
WBC: White Blood Cell, PC: Platelet Count, ALC: Absolute Lymphocyte Count, ANC: Absolute Neutrophil Count, AMC: Absolute Monocyte Count, NLR: Neutrophil to Lymphocyte Ratio, MLR: Monocyte to Lymphocyte Ratio, PLR= Platelet to Lymphocyte Ratio, MPV: Mean Platelet Volume			

Table 3 Hematological parameters of patients whose repetitive samples were received on admission and at the time of discharge/death of the COVID-19 positive patients

Hematological Parameter		Mean ± SD	p-value
Pair 1	PLT_b	198.78 ± 98.12	0.753
	PLT_a	245.83 ± 106.53	
Pair 2	WBC_b	8.24 ± 5.05	0
	WBC_a	8.33 ± 5.02	
Pair 3	NEU_b	63.70 ± 15.72	0.859
	NEU_a	63.56 ± 14.41	
Pair 4	LYM_b	26.78 ± 13.80	0.111
	LYM_a	27.85 ± 12.71	
Pair 5	MON_b	5.85 ± 6.34	0.058
	MON_a	5.44 ± 2.44	
Pair 6	EOS_b	1.85 ± 4.56	0.02
	EOS_a	2.23 ± 4.70	
Pair 7	NLR_b	3.29 ± 2.13	0.219
	NLR_a	3.09 ± 1.92	
Pair 8	MLR_b	0.27 ± 0.37	0.237
	MLR_a	0.23 ± 0.12	
Pair 9	PLR_b	9.67 ± 5.34	0.004
	PLR_a	10.65 ± 4.53	
Pair 10	BAS_b	1.64 ± 1.21	0.058
	BAS_a	1.0 ± 1.19	
N=225, b: On admission, a: before discharge/death. WBC: White Blood Cell, NLR: Neutrophil Lymphocyte Ratio, MLR: Monocyte Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio			

On comparing the haematological parameters of survived and non-survived patients we found that the difference between WBC (p=0.000), lymphocyte count (p=0.001), neutrophil count (p=0.001), and NLR (p=0.006) were statistically significant with a p-value of <0.025. The patients who died had higher WBC count (mean=9996/µl) and lymphopenia (25.19%) in comparison to those who survived (mean WBC=7656/µl and Lymphocyte=30.34%). They also had higher neutrophil count and NLR than survived patients (Table 4).

Table 4 Hematological parameters of survived and expired COVID-19 positive patients along with the significance

		Mean ± Std. Deviation	Sig. (2-tailed)
1	**Platelet S**	194.97 ± 123.398	0.206
	Platelet E	175.33 ± 101.072	
2	**WBC S**	7.66 ± 4.4307	0
	WBC E	9.99 ± 5.3866	
3	**Neutrophil S**	59.91 ± 13.081	0.001
	Neutrophil E	65.45 ± 13.663	
4	**Lymphocyte S**	30.34 ± 11.811	0.001
	Lymphocyte E	25.19 ± 12.518	
5	**Monocyte S**	6.02 ± 4.925	0.9
	Monocyte E	5.94 ± 4.926	
6	**Eosinophil S**	2.50 ± 2.502	0.726
	Eosinophil E	3.51 ± 3.519	
7	**Basophil S**	1.13 ± 2.434	0.285
	Basophil E	1.49 ± 2.471	
8	**MLR S**	0.31 ± 1.735	0.971
	MLR E	0.30 ± 0.309	
9	**PLR S**	8.40 ± 8.743	0.58
	PLR E	9.02 ± 7.999	
10	**NLR S**	2.66 ± 2.501	0.006
	NLR E	3.59 ± 2.757	

N: 225, S: Survived, E: Expired. WBC: White Blood Cell, NLR: Neutrophil Lymphocyte Ratio, MLR: Monocyte Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio

DISCUSSION

The burden of COVID-19 patients is dramatically increasing with time. The clinical features and epidemiology show that it has a wide clinical spectrum ranging from asymptomatic infection to severe pneumonia with acute respiratory failure and even resulting in death. However, the epidemiological curve of COVID-19 patients is not fully illustrated in the Indian population due to a lack of data regarding the asymptomatic and mildly symptomatic cases. In our study also we had included all the symptomatic patients who visited the tertiary care hospital which is a small proportion of the truly infected cases.

At present, the early identification of severely ill patients is very important for the timely triaging of these patients. In this study, we have analyzed various haematological parameters which can be helpful in this triaging.

Demographic Characteristics

The present study showed that males are more affected than females, which was similar to other studies conducted by Guan, et al., Zhang, et al. and Nanshan, et al. [9-11]. Studies conducted on MERS and SERs COV previously had also shown more susceptibility to infection in males than females [12-13]. The increased susceptibility in males may be due to less adaptive and innate immunity in males in comparison to females in whom the X chromosome and sex hormones play an important role in immunity development [14].

A study conducted in Wuhan, China by Li, et al. on 425 patients showed that all cases were adults ranging from 15-89 years [15]. There were no pediatric cases in their study. Another study conducted by Tiwari, et al. in the Indian population which included 32 cases showed that 12.9% of cases were of the pediatric age group [16]. The present study had only 2.17% of pediatric cases this difference could be due to the small population size included by Tiwari,

et al. as well as immunological, ethical, or racial variation among the cases [16].

Hematological Findings in COVID-19 Patients

White blood cell count: The mean WBC count of all the patients was 7670 cells/µl which was within the normal baseline range. We found that two patients had leucopenia, six had leucocytosis and the rest had normal counts. This finding was similar to Lui, et al. in which the WBC count was within the normal range (4600 cells/µl) whereas it was in contrast to the previous study by Lippi, et al. who reported leucocytosis, neutrophilia, and lymphopenia in Covid-19 patients [17,18]. We studied the trend of WBC on the first and last day of hospital admission of Covid-19 positive patients and found that there was a slight increase in the WBC count but the counts were still within the normal range. This difference in WBC count on the first day and last day of hospitalization was not statistically significant. The rise of WBC count in survived patients was not significant. When the WBC count was compared between the survived and non-survived patients we found that those who expired had leucocytosis and the difference was highly significant (p=0.000). This result is similar to the results of a study by Lippi G, et al. [18]. The present study shows that WBC count can be helpful in the prediction of progression of disease from mild to severe and then to critical stages of Covid-19 disease.

Lymphocyte Count: The lymphocyte count when analyzed in all the patients was within normal ranges. When they were compared between the first and last visit of the patients then also no significance was detected while on further comparison between the survived and non-survived patients we found the non-survived cases had lymphopenia (p=0.001). Yang, et al. and Huang, et al. also reported that 85% of the critically ill patients in their study showed lymphopenia [19,20]. Another study by Bai, et al. also mentioned that critically ill Covid positive patients had lymphopenia with a median lymphocyte count of 800 cells/µl [21]. A study done in Zhongnan Hospital of Wuhan University recorded lymphocyte count in COVID-19 patients who died and found that in comparison of survived patients they had significant lymphopenia [22]. Lymphocytes are the major antiviral cells that were found to be prone to decrease continually in severely ill Covid-19 patients. In SARS both CD4 and CD8 positive T-lymphocytes are reduced. The lung injury model of SARS-CoV in BALB/c mice revealed that IFN-I sensitizes virus-specific T-cells (CD4+ and CD8+) to apoptosis by up-regulating Fas and Fas ligand on T-cells resulting in lymphopenia [23]. It was mentioned in previous studies that peripheral blood from dead patients showed decreased CD4+ and CD8+ T cells as well as increased HLA DR and CD38+ T double-positive cells by flowcytometry reflecting hyperactivation of lymphocytes before exhaustion [24].

ACE2 (Angiotensin Converting Enzyme 2) acts as the receptor for both SARS-CoV-2 and SARS-CoV to infect cells [25]. ACE and ACE2 are homologs with different functions in the Renin-Angiotensin System (RAS) [26]. Some studies reflect the possibility of the role of ACE in regulating hematopoiesis. In Covid-19 infections, ACE2 receptors are reduced resulting in up-regulation of ACE in myeloid precursors facilitating increased production of pro-inflammatory myeloid cells and macrophages with activation of T-cells and decreased production of myeloid suppressor cells. This also results in increased consumption of T-cells and causes lymphopenia.

Neutrophil Count and Neutrophil Lymphocyte Ratio (NLR): A study conducted by Huang, et al., Wang, et al. and Liu, et al. showed evidence of neutrophilia in critically ill Covid19 positive patients admitted in ICU [17,19,22]. In a study by Huang, et al. the median ANC (Absolute Neutrophil Count) of ICU and non-ICU patients with COVID-19 was 4.6 (2.6-7.9) × 10^9/L and 2.7 (1.9-3.9) × 10^9/L, respectively [19]. Whereas the median ANC in a study by Wang, et al. in ICU cases was 10.6 (5.0-11.8) × 10^9/L and 4.4 (2.0-6.1) × 10^9/L in non-ICU cases (p=0.00069) [22]. Similarly another study by Liu, et al. also showed higher neutrophil count in critically ill patients than in non-critically ill patients with a p-value of 0.025. In the present study also the ANC was significantly higher in non- survived patients(6.54 × 10^9/L) than the survived patients (4.59 × 10^9/L) with p=0.001.

Lui, et al. also studied NLR in 61 cases and found that it was a predictor marker of critical illness. They divided the cases into two groups based on the cut-off value of NLR (low risk, <3.13; high risk, ≥ 3.13) and age (<50 years or ≥ 50 years). It was stated that patients with age ≥ 50 years and high-risk NLR had severe illness (p=0.0195) [17]. In the present study, we noted that the NLR was higher in non-survived cases (3.59) than in survived cases (2.56) with a p-value of 0.006. However, in survived patients on follow up NLR did not show any significant difference with recovery. NLR is a biomarker for the assessment of the prognosis of bacterial infections and malignancies. It can also serve as an early predictor marker of severity of illness in Covid-19 positive cases.

Eosinophil count: The covid-19 positive cases had lower eosinophil count when first visited the hospital which was increased on recovery on follow up. This difference was significant with p=0.025. A study by Xu, et al. has highlighted that eosinopenia is an important prognostic factor in these cases [27]. Another Indian study by Tiwari, et al. revealed that they had 25.8% Covid-19 positive cases with eosinopenia in their study [16]. However, when we analyzed the eosinophil count in survived and non-survived cases we found that although the count was lower in non-survived patients the difference was not significant (p=0.726). Thus, this parameter requires further studies for the assessment of its importance as a prognostic marker.

Monocyte count and Monocyte Lymphocyte Ratio (MLR): Monocytosis was noted only in a single study by Tiwari, et al. in 16.5% cases. No other study documented monocytosis previously other than this. In our study monocytosis was noted in only 8 cases out of 829 (9.65%). On follow-up, the trend of monocyte count was not significant. Also, there was no significant difference noted amongst survived and non-survived patients.

The monocyte to lymphocyte ratio was not previously studied in any of the studies. In the present study, the difference of MLR on subsequent visits in survived cases was statistically significant with a p-value of 0.004. This parameter also requires further studies for the assessment of its importance as a prognostic marker.

Platelets and platelet to lymphocyte ratio: A study by Li, et al. concluded that thrombocytosis along with longer hospital stay might be related to cytokine storm in COVID19 positive cases [28]. In these cases, PLR reflects the degree of cytokine storm and this can provide a new biomarker for monitoring of COVID-19 cases [28]. In the present study, only one case had thrombocytopenia and 3 had thrombocytosis. The mean platelet count of all the COVID-19 positive cases was within the normal reference range. On subsequent follow up the platelet count was significantly increased on recovery of cases than the baseline values when they were admitted with COVID-19 infection (p=0.000). On analyzing the survived and non-survived cases, the platelet counts were lower in expired cases than those of survived but this difference was not significant (p=0.206). Previous studies conducted in China showed that COVID-19 is associated with thrombocytopenia ranging from 5% to 57% of cases [19,29,30].

Reduction of platelet count may be attributed to lung damage which results in decreased production of platelets. As we know lung is a reservoir of megakaryocytes and acts as a potential hematopoietic organ that produces 50% of total platelets. Lung damage also activates the coagulation cascade resulting in increased consumption of platelets, thus resulting in thrombocytopenia [31].

Platelet to Lymphocyte Ratio (PLR) was found to be higher in severe patients than in non-severe patients by Rang, et al. [32]. They revealed that the patients with higher PLR had longer stay in the hospitals. They showed that PLR in non-severe patients and severe patients were 242.75 and 160.02 respectively with a p-value of 0.414 but when they compared PLR at its peak the difference was very significant(p=0.001). In our study, the PLR in non-severe patients and severe patients were 840.34 and 901.60 respectively with a p-value of 0.580. The difference of PLR in both groups was not significant but was higher than those of Rang, et al. Similarly on follow-up of the survived cases the difference of PLR on first and last visit was also not significant (p=0.058). Previous studies indicate that PLR is a biomarker of severity of inflammation in diabetes, coronary heart disease, connective tissue diseases, and tumors. The increase of PLR is directly related to the size of the tumor, lymph node infiltration, distant metastasis, and prognosis. It is an effective biomarker for the clinical diagnosis and prognosis of community-acquired pneumonia [33]. As PLR includes both platelet and lymphocyte count it indirectly represents both platelet aggregation and inflammation and it may be a more reliable marker in predicting prognosis rather than platelet and lymphocyte count. In our study, the PLR was raised in severe patients but was not significantly raised. This may be due to effective treatment of thrombocytopenia and timely control of inflammation in severely ill patients in our intensive care units along with regular platelet transfusion.

The IFCC guidelines indicate that the CBC parameters in a Covid-19 positive case show leucocytosis with neutrophilia, lymphopenia, and thrombocytopenia. Some recent publications show that RBC count and haemoglobin levels are affected by SARS-CoV2 but our study did not show any significant changes in these two parameters.

CONCLUSION

The present study included a large number of patients and showed that the baseline CBC parameters are not much affected in COVID-19 positive patients but the parameters like WBC count, Lymphocyte count, neutrophil count, and

NLR are significantly higher in non-survived patients. These parameters can serve as biomarkers in predicting the prognosis and severity of the disease. This study also highlights that single-time PLR cannot be used as an indicator of disease progression and a repeat PLR is required for the final assessment.

DECLARATIONS

Conflicts of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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