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ORIGINAL RESEARCH

Hematologic profile in covid-19 positive patients: A retrospective study

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ABSTRACT

Background: COVID-19 is an ongoing global pandemic. Alterations in hematological profile in patients with COVID-19 are developing as significant features of the disease. A complete blood workup as well as continuous tracking of hematological parameters play a vital role in revealing the risks of disease progression and eventually help in better treatment and outcome. **Objective:** To co-relate the hematologic profile in covid-19 positive patients with respect to need of ICU. **Methods:** This retrospective study was carried out in Laboratory (Pathology Department), Government Medical college, Jammu, India. In this study, 100 patients who were confirmed as COVID-19 positive by real-time- PCR from whom a nasal swab was obtained and those who were thereafter hospitalized with an initial diagnosis of COVID-19 were studied retrospectively. **Results:** In the present study we have enrolled 100 patients in which 61.0% patients were male and the 44.0% patients belonging to 36-50 years age group with mean age 42.42±11.428.On comparing the laboratory parameters of the Non-ICU and ICU covid-19 positive patients it was found that WBC count, neutrophil, neutrophil to leucocyte ratio, prothrombintime, C-reactive protein and serum ferritin were was significantly higher in ICU group ($p<0.05$).The cutoff value of WBC count, neutrophil, neutrophil to leucocyte ratio, prothrombin time, C-reactive protein, serum ferritin, leucocyte and platelet were 6.91, 5.5, 5.81, 14.5, 59.0, 780.0, 0.73 and 1.55respectively.The accuracy of the laboratory variables were 78.4%, 91.0%, 96.7%, 86.5%, 78.7%, 83.2%, 87.0% and 77.3% respectively. **Conclusion:** Rapid blood tests, WBC count neutrophil, neutrophil to leucocyte ratio, prothrombin time, C - reactive protein and serum ferritin can help clinicians to assess need of ICU with COVID-19 positive patients.

Key words: COVID-19, neutrophil lymphocyte ratio, Prothrombin - Time, C - reactive protein, Serum ferritin.

INTRODUCTION

In December 2019, a crowd together of patients existed with an unknowntype of viral pneumonia in Wuhan, China, with common history of visiting the Huanan seafood market. The virus was isolated from biologic sample and recognized as genus beta-coronavirus, introduction it at the side of other severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)[1]. SARS-CoV-2 is an enveloped, non-segmented, RNA virus responsible for the 2019 coronavirus disease (COVID-19) pandemic [2].The occurrence of COVID-19 has been affectinglarge global health distress, with the world silentassembled information as regards the transmission dynamics andspectrum of illness. The increasing number of COVID-19 infections may be attributable to the late identification of source of infection and the capability of host to discard the virus while being asymptomatic [3].

A complete blood workup as well as continuous tracking of hematological parameters play a vital role in revealing the risks of disease progression and eventually help in better treatment and outcome. CBC is easily performed and inexpensive. Included in CBC are profile such as TLC, neutrophil and lymphocyte. These can be act as inflammatory markers. Neutrophils are the a large amountfeatures cell type with the white blood cells and are an imperativeconstituent of the immune system. The role of lymphocytes in both inflammation and infection is evident [4].

Serum ferritin is an iron storage protein that is widely measured as an indicator of iron status, but it also a well-known inflammatory marker. Serum ferritin levels can be increased significantly in response to inflammation. In 1997, Connelly et al. discovered the serum ferritin level in patients at possibility for

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ARDS and found serum ferritin to be a predictor of ARDS [5].

This speedy viral extend has encouraged the publication of plentiful studies to recognize clinical,biological, radiological, and genetic indicators for the evolution to severe and incurable formsof the disease [6]. Demographic (advanced age, male sex), clinical (co-morbidities,acute respiratory distress syndrome [ARDS]), and radiological predictors have beenextensively detailed in different studies [6].Biological (lymphopenia, hyper-ferritinemia,serum C-reactive protein [CRP] levels) predictors have been reported [6,7].

Our study enriches these data by exposure the knowledge in our developing country,which undertook captivityprocedures at an early phase of the disaster, thereby impacting theevolution of this pathology. The objective of our study was to describe the hematological abnormalities in our study patients with COVID-19 and to identify the parametersthat can help distinguish those likely to develop severe COVID-19.

MATERIAL & METHODS

This retrospective study was carried out in Laboratory (Pathology Department), Government medical college & hospital, Jammu, India. In this study, 100 patients who were confirmed as COVID-19 positive by real-time- PCRfrom whom a throat swab was obtained and those who were thereafter hospitalized with an initial diagnosis of COVID-19 were studied retrospectively. Both ICU and Non-ICU patients both sex with greater than 18 years of age patients were included in the study.

We collected blood from patients with COVID-19 using the routine methods and evaluated haematological parameters. The blood samples were run in the Central laboratory ofGovernment medical college & hospital, Jammu, Jammu & Kashmir by the laboratory technician and the CBC, CRP and Serum Ferritin results obtained were studied and approved by a Consultant Pathologist.

Complete blood count(CBC) was determined by using Horiba Pentra DX Nexus hematology analyzer; C - reactive protein was determined with a commercial kit (Abbott Laboratories) and analyser (Architect C8000; Abbott Laboratories) and Serum Ferritin levels were determined using Siemens Dimension EXL analyzer.

The analysis of the data was done using the IBM SPSS 25.0 statistical package programs. A Chi-square test was used to analyze the categorical variables of the patients, which were expressed as a number and percentage. For parametric continued variables, the independent samples t-test was used for analysis and they were presented as a mean and standard deviation. A receiver-operating characteristic(ROC) curve was generated, to find cut-off values in the diagnosis of critical cases of COVID-19 and thearea under the curve (AUC) was calculated. A two-tailed $p< 0.05$ was considered statistically significant.

OBSERVATION

In the present study, we have enrolled 100 patients in which 61.0% of patients were male and 44.0% patients belonging to the 36-50 years age group with a mean age of 42.42±11.428 years (range: 18-70 years). 66.0% of patients had no comorbidity while Diabetes +HTN in 10.0%, HTN in 8.0%, Diabetes and Diabetes +HTN+CHD in 4.0% each. 93.0% of patients presented fever followed by cough in 86.0%, Shortness of breath in 44.0%, fatigue in 38.0%, myalgia in 20.0%, diarrhea in 15.0%, and Nausea or vomiting were in only 8.0% covid-19 positive patients (Table No. 1). Out of 100 patients, 28 patients had admitted to the ICU, and 72 patients did not need ICU support.

On comparing the hematological parameters in between Non-ICU and ICU admitted patients with positive covid-19, we found that WBC count, neutrophil, neutrophil to leucocyte ratio, prothrombin time, C-reactive protein, and serum ferritin were was significantly higher in the ICU group ($p<0.05$). In contrast, leucocyte and platelet were significantly lower in the ICU group (<0.05). Hemoglobin showed an insignificant difference in both groups (Table No-2). The receiver operating curve (ROC) showed that the cut-off value of WBC count, neutrophil, neutrophil to leucocyte ratio, prothrombin time, C-reactive protein, serum ferritin, leucocyte, and platelet were 6.91, 5.5, 5.81, 14.5, 59.0, 780.0, 0.73 and 1.55 with the area under the curve 0.784, 0.910, 0.967, 0.865, 0.787, 0.832, 0.870 and 0.773 respectively, to predict the need of ICU in covid-19 positive patients.

At the above cutoff point the sensitivity of WBC count, neutrophil, neutrophil to leucocyte ratio, prothrombin time, C-reactive protein, serum ferritin, leucocyte and platelet were 82.1%, 96.4%, 100.0%, 92.9%, 89.3%, 92.9%, 90.3% & 84.7% and specificity was 47.2%, 51.4%, 47.2%, 50.0%, 40.3%, 50.0%, 57.1% & 50.0% with the accuracy 78.4%, 91.0%, 96.7%, 86.5%, 78.7%, 83.2%, 87.0% and 77.3% respectively (Table No. 3 and 4). The values above the cutoff point in the parameter of WBC count, neutrophil, neutrophil to leucocyte ratio, prothrombin time, C-reactive protein, and serum ferritin which indicates the need of ICU while in case of leucocyte and platelet the value below the cutoff point shows the need of ICU (Table No. 5).

Table No. 1: Demographic characteristics of the studied patients

		Frequency (n=100)	Percentage
Age (Years)	**<= 35**	29	29.0%
	36 - 50	44	44.0%

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	51+	27	27.0%
Mean Age±SD (Min to Max) Years		42.42±11.428(18-70)	
Sex	**Male**	61	61.0%
	Female	39	39.0%
Comorbidity	**No comorbidity**	66	66.0%
	Diabetes+HTN	10	10.0%
	HTN	8	8.0%
	Diabetes	4	4.0%
	Diabetes+HTN+CHD	4	4.0%
	HTN+CHD	2	2.0%
	Others	6	6.0%
Signs and symptoms	**Fever**	93	93.0%
	Cough	86	86.0%
	Shortness of breath	44	44.0%
	Fatigue	38	38.0%
	Myalgia	20	20.0%
	Headache	18	18.0%
	Diarrhea	15	15.0%
	Nausea or vomiting	8	8.0%

Table No. 2: Hematological findings of the patients on admission

Hematological variables	Non-ICU (n=72)	ICU(n=28)	P value
Hemoglobin (gm%)	12.15±0.81	12.53±1.04	0.086
WBC (10^9 cells per L)	6.78±1.40	8.65±1.855	**<0.001**
Neutrophil (10^9 cells per L)	5.36±1.07	7.72±1.56	**<0.001**
Leucocyte (10^9 cells per L)	0.97±0.19	0.66±0.21	**<0.001**
Neutrophil to Leucocyte Ratio	5.64±1.27	13.29±5.97	**<0.001**
Platelet (10^9 cells per L)	2.07±0.54	1.45±0.50	**<0.001**
ProthrombinTime (S)	14.35±1.10	16.93±2.04	**<0.001**
CRP (mg/L)	57.56±23.42	100.06±43.63	**<0.001**
S. Ferritin (µg/L)	730.64±194.78	1077.89±307.45	**<0.001**

Student t test; P value <0.05 = Significant; P>0.05 = Insignificant

Table No. 3: ROC Curve (Area under the Curve)

Test Result Variable(s)	Area under Curve	Std. Error[a]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
WBC (10^9 cells per L)	0.784	0.052	0.683	0.885
Neutrophil (10^9 cells per L)	0.910	0.032	0.847	0.973
NL Ratio	0.967	0.021	0.925	1.000
Prothrombin Time (S)	0.865	0.042	0.784	0.947
CRP (mg/L)	0.787	0.051	0.687	0.888
S. Ferritin (µg/L)	0.832	0.044	0.745	0.919
Leucocyte (10^9 cells per L)	0.870	0.041	0.790	0.951
Platelet (10^9 cells per L)	0.773	0.053	0.669	0.877
The test result variable(s): WBC, Neutrophil, Leucocyte, NL Ratio, Platelet, Prothrombin Time, CRP, S. Ferritin has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.				
a. Under the nonparametric assumption				

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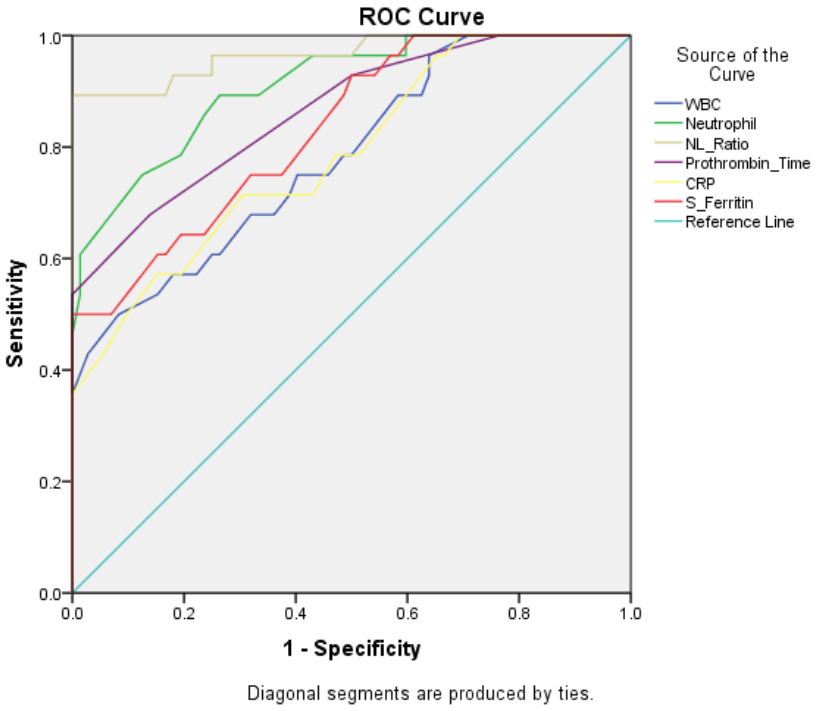

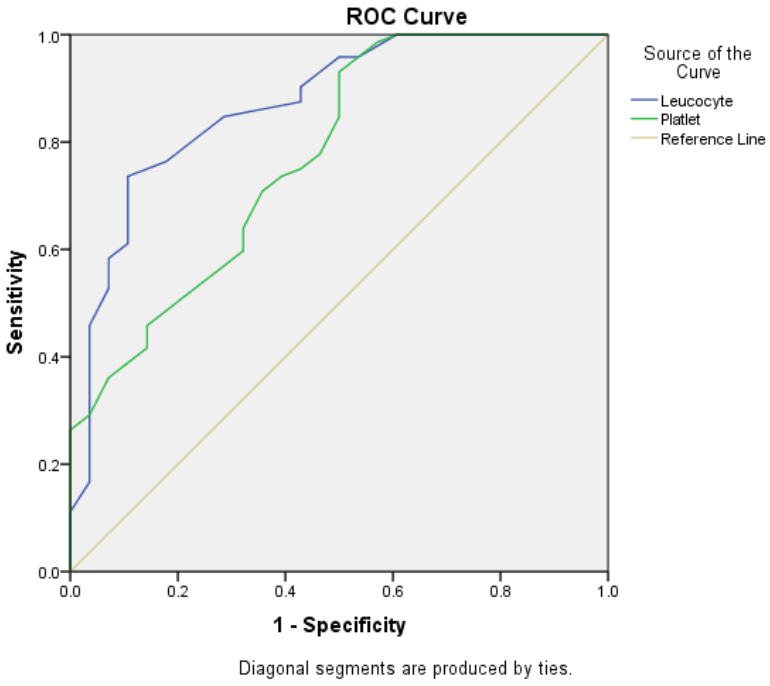

Table No. 4:Cut-off values for significant markers in the prediction of Corona virus -disease in studied patients

Hematological Variables	Cutoff value	Sensitivity	Specificity	Accuracy
WBC (10^9 cells per L)	6.91	82.1%	47.2%	78.4%
Neutrophil (10^9 cells per L)	5.5	96.4%	51.4%	91.0%
NL Ratio	5.81	100.0%	47.2%	96.7%
Prothrombin Time (S)	14.5	92.9%	50.0%	86.5%
CRP (mg/L)	59.0	89.3%	40.3%	78.7%
S. Ferritin (µg/L)	780.0	92.9%	50.0%	83.2%
Leucocyte (10^9 cells per L)	0.73	90.3%	57.1%	87.0%
Platelet (10^9 cells per L)	1.55	84.7%	50.0%	77.3%

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Table No. 5: Distribution of Covid-19 patients according to cut-off points

Hematological Variables		Non-ICU (n=72)	ICU (n=28)	Likelihood Ratio	P value
WBC(10^9 cells per L)	**≤6.91**	34 (47.32%)	5 (17.9%)	7.882	**0.007**
	>6.91	38 (52.8%)	23 (82.1%)		
Neutrophil(10^9 cells per L)	**≤5.5**	41 (56.9%)	1 (3.6%)	29.010	**<0.001**
	>5.5	31 (43.1%)	27 (96.4%)		
Leucocyte(10^9 cells per L)	**≤0.73**	7 (9.7%)	16 (57.1%)	23.686	**<0.001**
	>0.73	65 (90.3%)	12 (42.9%)		
NL Ratio	**≤5.81**	34 (47.2%)	0 (0.0%)	28.616	**<0.001**
	>5.81	38 (52.8%)	28 (100.0%)		
Platelet(10^9 cells per L)	**≤1.55**	11 (15.3%)	14 (50.0%)	12.091	**<0.001**
	>1.55	61 (84.7%)	14 (50.0%)		
ProthrombinTime (S)	**≤14.5**	36 (50.0%)	2 (7.1%)	18.590	**<0.001**
	>14.5	36 (50.0%)	26 (92.9%)		
CRP (mg)/L	**≤59.0**	29 (40.3%)	3 (10.7%)	9.232	**0.004**
	>59.0	43 (59.7%)	25 (89.3%)		
S. Ferritin(µg/L)	**≤780**	36 (50.0%)	2 (7.1%)	18.590	**<0.001**
	>780	36 (50.0%)	26 (92.9%)		

Likelihood Ratio and chi square test; P value <0.05 = Significant; P>0.05 = Insignificant

DISCUSSION

SARS-CoV-2 has spread rapidly across many countries and has a wide spectrum of severity. Although most COVID-19 patients have mild to moderate courses, up to 5–10% can have severe, likely life-threatening diseases [8]. Isolating confirmed COVID-19 cases and extensive tracing of contacts with their early testing can help in breaking the chain of transmission among population and control this pandemic.

In the present study, we have enrolled 100 patients in whom 61.0% of patients were male and 44.0% patients belonging to the 36-50 years age group with a mean age of 42.42±11.428 years. Recent studies were also reported that Covid-19 is seen more frequently in males and above 40 years age category [4,9,10].The most common comorbidities were hypertension, obesity, COPD and diabetes which are similar to our study [11,12].

In the present study, 28% patients were admitted in ICU due to severe condition. Similarly in the study by Hunag C et al [13]. and Wang D et al. [14] reported 31.7% and 26% rate of requirement of ICU respectively. Recently Asian study was reported the rate of requirement of ICU support in severe cases were 22% which was lower than the present study [15].The ICU patients had a relatively higher proportion of male and were relatively older which is consistent with previous study [16,17].This suggests that age, gender and comorbidity may be risk factors for poor outcome.

Patients who underwent ICU care had numerous laboratory abnormalities than non- ICU patients. These abnormalities suggest that covid-19 infection may be correlated with cellular immune deficiency, coagulation activation, myocardia injury, hepatic injury, and kidney injury. These laboratory deformities are also comparable to those previously discussed in patients with MERS-CoV and SARS-CoV infection. On comparing the haematological parameters in between Non-ICU and ICU admitted patients with positive covid-19, we found that WBC count, neutrophil and neutrophil to leucocyte ratio, prothrombin time were significantly higher in the ICU group ($p<0.05$). Liao D et al [18] also found elevated neutrophil to lymphocyte ratio as a useful predictor for severity and mortality of SARS-CoV-2 infection. A study of Yang AP et al [19] who concluded that high neutrophil to lymphocyte ratio and age are the independent factors for indicating poor clinical outcome of covid-19 patients. While Fan BE et al [20] found leukopenia (WBC ≤4 x 109/L) in almost 19% of the total admitted patients, out of which only one person presented with sever leukopenia. Lymphopenia was also featured in these patients which was associated with the severity of disease. Hemoglobin showed no association with severity of disease in Covid-19 patients [21].

We also found a significantly increased C-reactive protein level and serum ferritin in severe and critical patients ($P<0.05$). In a retrospective cohort study from Wuhan, China, Terpo E et al. [21].reported that increased ferritin was a risk factor for Acute Respiratory distress syndrome, ICU support, and mortality.Similarly, in the Pakistani study by Taj S et al. [22],serum ferritin and CRP values were significantly increased in severe and critical patients compared to mild and moderate patients. The rise in CRP levels reflects the extent of the systemic inflammatory syndrome seen in severe types of the disease, followed by a massive release of inflammatory cytokines producing a "cytokine storm" liable for acute tissue damage, including subsequent multi-systemic failure and onset of severe ARDS [23].

In the results of this study, which are also consistent with previous research, low thrombocyte and leukocyte counts were revealed in severe COVID-19

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positive patients. Thus, it can be said that thrombocytopenia and leukopenia may be indicative of COVID-19 disease. Likewise, thrombocytopenia and leukopenia were noted in Guan et al.'s study [24].The thrombocyte count was also found to be low in the study by Assiri et al. [25] and leukopenia was noted in another study conducted by Xu et al.[10].Lymphopenia has been adequately described in a retrospective analysis of patients in Hong Kong and Singapore affected with SARS-COV in 2003 and was correlated with unfavorable outcome and ICU stay [26,27].

Analysis of coagulation profile showed that the incidence of abnormalities in conventional coagulation function parameters were higher in patients with ICU group compared to non-ICU group. This finding is consistent with previous reports. [10,28]. Similar findings were observed by Iba T et al. [29]assessed that PT and APTT were either normal or deranged in the patients with COVID-19 infection, and these parameters depended upon the extent of coagulopathy as well as its association with other co-morbidities like Hemolytic Uremic Syndrome, Thrombotic Thrombocytopenic Purpura,Antiphospholipid Syndrome, Sepsis Induced Coagulopathy and Disseminated Intravascular Coagulopathy.

In this study, the prognostic value of laboratory indicators was analysed by using ROC curve. The AUC of WBC count, neutrophil, neutrophil to leucocyte ratio, prothrombin time, C-reactive protein, serum ferritin, leucocyte and platelet ranged from 0.773 to 0.967. The AUC of neutrophil to leucocyte ratio was the largest. The optimal working point was 5.81, and the sensitivity and specificity to predict the prognosis of severity of disease in patients infected with COVID-19 were 100% and 47.2%, respectively.

The AUC of laboratory parameters such as CRP, serum ferritin, leucocyte and prothrombin time indicated that they could be used to predict the presence of COVID-19 disease, while those of platelet and WBC were near the reference line of ROC curve, indicating that they were poor predictors of the disease. In the study by Zhang et al. [30] NLRs were used as an early diagnostic marker for aiv-H7N9 patients. Ai-Ping Yang et al.[31]found an AUC of 0.743, with a cut-off of 3.3, specificity of 0.636, and a sensitivity of 0.88 for NLR in determining the prognosis for seriously ill COVID-19 patients. CRP is also a useful inflammatory marker and indicator that play an essential role in host resistance to invasive pathogens and inflammation [32]. CRP is highly correlated with acute lung injury in 2019-nCoV-infected patients [33]. Besides, higher CRP and PT levels are linked to adverse aspects of COVID-19 diseases, such as acute respiratory distress syndrome development, cardiac injury, and casualty [34]. Therefore, the detection of hematological parameters levels in the severe COVID-19 patients could assess the need for ICU support.

Study limitations

The single-center retrospective study design, which increases the risk of selection bias and influences the generalizability of data; immunological parameters were not evaluated (CD4, CD8, interleukin-6, interleukin-8, interleukin-10), which could help us to investigate the inflammatory characteristics of our patients properly; the small sample size and missing data from some paucisymptomatic patients and patients who died at a given time. Further, a multicenter study with a large sample size should be conducted comparing patients' onset of symptoms and correlating their clinical condition to laboratory findings

CONCLUSION

Predictors of a fatal outcome in severely infected patients with COVID-19 included WBC count, neutrophil, neutrophil to leucocyte ratio, prothrombin time, C-reactive protein, serum ferritin, leucocyte, and platelet. Among them, the neutrophil to leucocyte ratio was the strongest individual predictive laboratory predictor. COVID-19 is a systemic infection with a significant impact on the haematopoietic system and haemostasis. Careful evaluation of laboratory parameters at baseline and during the disease course can assist clinicians in formulating a tailored treatment approach and promptly provide intensive care to those in greater need. Larger analysis confirming these findings and investigating the pathophysiology and impact of the correction of coagulopathy on mortality are warranted.

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