Original Article

Clinico-haematological profile in COVID-19 patients –an observational study at tertiary care centre

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ABSTRACT

Background: It is known as in other viral infections, severe acute respiratory syndrome coronavirus 2 infections, can be associated with haematological changes and often has the potential to optimize the monitoring of the infectious process and their severity. Hence, we took up this study to analyze clinico-haematological profiles in coronavirus disease-2019 patients and to compare haematological changes between mild, moderate, and severe cases.

Materials and Methods: The study included the patients who were tested positive for coronavirus disease-2019 infection and the patients were classified into mild, moderate and severe cases. The demographic data and the laboratory haematological parameters were collected and statistically analysed. The median values were compared between mild, moderate, and severe cases using non-parametric tests, Kruskal-Wallis test with posthoc Mann-Whitney, and the p-value was calculated using Chi-square test for statistical significance.

Results: Data was collected for 276 patients, of which 167 patients were mild cases, 50 were moderate and 59 were severe. The median was derived for all the haematological parameters in mild, moderate, and severe groups which showed an increasing trend in total leucocyte count, absolute neutrophil count, neutrophil to lymphocyte ratio, and a decreasing trend in absolute lymphocyte count and statistically significant with p-value <0.05.

Conclusions: Coronavirus disease-2019 infection is associated with changes in haematological parameters, as the severity of the disease progresses total leucocyte count, absolute neutrophil count, and neutrophil to lymphocyte ratio increase but absolute lymphocyte count decreased. High neutrophil to lymphocyte ratio and lymphopenia are valuable early risk stratification parameters.

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INTRODUCTION

Coronavirus disease-2019(COVID-19) is an acute respiratory and systemic disease caused by novel coronavirus SARS-CoV-2 and is declared as a global pandemic by WHO on 11th March 2020. As the pandemic is progressing over time, India has reported over 8,85,92,919 cases so far with as many as 1,36,696 death as of 29th November 2020 as per the Ministry of Health and Family Welfare Government of India(MOHFWGOI) website data.[1] Various haematological parameters alteration has been documented in the current literature review in SARS-CoV-2 infection primarily from the adult cases in Chinese

and Western population, which signifies the severity and the prognosis of the patient outcome.[2] As per the Diagnosis and Treatment Guidelines (trial version 7) review, in the early stage of the disease onset total leucocyte count(TLC) is normal and the lymphocyte count is reduced.[3] From a study conducted by Li T et al[4] & Sharma D et al[5] the absolute lymphocyte count(ALC) was found to be inversely related to the severity of patients which in turn could be used to predict the prognosis of patients with COVID-19. Liu J et al[6] found that the neutrophil-to-lymphocyte ratio(N/L ratio) predicts critical illness in patients infected with COVID-19. Fan BE et al[7] compared haematological parameters in ICU and non-ICU patients and showed that on admission older age, lymphopenia, and raised lactate dehydrogenase(LDH) were associated with ICU admissions. Patients who were transferred to the ICU had a deeper nadir ALC, nadir haemoglobin(Hb), and higher peak ANC and peak LDH levels as compared to patients who did not require ICU stay.

Available data suggest that several haematological parameters may change in the course of SARS-CoV-2 infection and that some of them can be considered significant predictors of unfavourable clinical outcomes, such as admission to ICU or even death. As there is paucity in the literature regarding detailed haematological evaluation in COVID 19 patients and their trend in mild, moderate, and severe cases and this study may help us know the severity predictors like high ANC, low ALC, high N/L ratio, and in triaging the patients who require oxygenated beds and ICU admission. Hence the present study was undertaken with the primary aim to assess the clinico-haematological profile in COVID-19 patients and the second objective of the study was to compare the haematological parameters and look for any statistical significance between mild, moderate, and severe COVID-19 patients.

MATERIALS AND METHODS

It was a single centre prospective study done at Vijayanagara Institute of Medical SciencesBallari, Karnataka India. Institutional ethical committee board approval was taken for performing the study. The diagnosis of COVID-19 was according to the MOHFWGOI guidelines and confirmed by reverse transcriptase-polymerase chain reaction(RT-PCR) or Rapid antigen testing(RAT) testing. Patients with symptoms related to COVID-19 were first tested with RAT, RAT negative, and asymptomatic primary contacts were tested with RT-PCR. RAT positive or RT-PCR positive were declared as COVID-19 positive. The study period was for six months from August 2020 to January 2021.

RT-PCR kit used was SD-Biosensor standard M nCoV real-time detection kit, it is a real-time reverse transcription-PCR assay for the qualitative detection of SARS-CoV-2 nucleic acids in nasopharyngeal and throat/oropharyngeal swab. This kit is based on TaqMan probe real-time fluorescent PCR technology. Coronavirus RNA was first transcribed

into cDNA by reverse transcriptase, and then cDNA was used as a template for PCR amplification. Qualitative detection of the new SARS-CoV-2 virus ORF1ab (RdRp) gene, E gene, and CY5 channel detection internal reference was done. Assessment of clinical specimen test results was performed after the positive and negative controls were examined and determined to be valid. Ct value <36 reported as SARS- COV-2 positive.

RAT kit used was Oscar SARS CoV-2 Corona antigen test kit using a nasopharyngeal swab. It is one step rapid qualitative sandwich immunoassay used for the detection of N antigen of coronavirus. The principle used is immunochromatography where monoclonal antibodies conjugated to colloidal gold and another monoclonal antibody is immobilized on a nitrocellulose membrane. If the sample contains coronavirus antigen, an antibody-antigen-antibody-colloidal gold complex is formed which shows a pink/purple T band within twenty minutes. The appearance of coloured bands at the T and C regions indicates that the sample is positive for SARS-CoV-2.

Inclusion criteria were COVID-19 positive patients admitted in COVID care center (level 1 for mild cases), dedicated COVID health care centre(DCHC, level 2 for moderate cases), and dedicated COVID hospital(level 3 for severe cases). Patients of all age groups were included in the study, from the data collected there were some paediatric and female patients but no pregnant patients recorded, and some of the patients had co-morbid conditions and drug history which were recorded in the data and analyzed. COVID-19 positive patients under home isolation were excluded from the study, as we could only collect the laboratory investigation details from hospitalized patients.

Demographic, clinical, and laboratory data were collected from the case sheets in the respective COVID wards. Mild or asymptomatic cases with SpO_2 (oxygen saturation) >94%, normal RR (Respiratory rate), and no evidence of pneumonia were admitted in COVID Care Centres(CCC). Moderate cases with SpO_2 90-94%, RR>24 bpm, pneumonia with no signs of severe disease were admitted to the dedicated COVID Health Care Centre(DCHC) with oxygen availability. Severe cases with SpO_2 <90%, RR >30bpm, and signs of severe pneumonia were in Dedicated COVID Hospital (DCH) with ICU facility and this is as per MOHFWGOI guidelines. The blood samples (2 mL) were collected in EDTA vacutainers and processed in either Sysmex XP100 or Erba H360 analyzers for a complete blood count. Hematological parameters reference values are Hb-Male 15+2g%, Female 13.5+1.5, TLC 4000-10,000/mm^3, ANC 2000-7000/mm^3, ALC 1000-3000/ mm^3, NLR 1.5-3.5, platelet count 1.5-4.5 lakh/ mm^3.[8] Limitation of our study was that there was no serial monitoring or follow up of the parameters, data was collected at once on the day of admission.

Data were entered in Microsoft office excel worksheets for mild, moderate, and severe cases. SPSS (Statistical Package for Social Sciences) version 20 was used to perform the statistical analysis. Descriptive statistics of the explanatory and outcome variables were calculated by a median, IQR (Interquartile range) for quantitative variables. Inferential statistics like the Kruskal-Wallis test were applied to check the statistical difference of Hb, TLC, N/L ratio, ANC, ALC, platelet count with posthoc Mann-Whitney for pairwise comparison. The Chi-Square test was applied for categorical variables. The level of significance was set for a P-value less than 0.05.

RESULTS

Of the 276 patients, 167 patients were in the mild, 50 were in the moderate, and 59 were in severe groups. Fever (77.8%), dry cough(48.5%), and breathlessness(32.9%) were the most common presenting symptoms in the mild group. In the moderate group, breathlessness(78%), fever(70%), and dry cough(50%) were common symptoms with which the patients presented to the Fever Clinics. Severe group had breathlessness(86.4%), fever(50.8%) and dry cough(49.2%) as most common presenting symptoms.

In mild cases, the age distribution was between 8-85 years with a median age of 45 years. Patients with moderate disease presented between 26-83 years with a median age of 60 years. Severe cases presented between 15-85 years with a median of 57 years. The highest number of cases were seen in the age group of 31-45 years(32.9%) and the least number of cases were seen in paediatric patients <15 years of age (1.8%) in mild cases. Moderate cases showed the highest number of cases in 46-60 years of age(40%) and no cases were noted in paediatric age group. Severe cases were highest in the age group of 46-60 years(47.5%) and no cases were seen in young adults (16-30 years). The age-wise distribution of cases showed statistical significance (p 0.000) (Table 1). The gender-wise distribution of cases showed male predominance in mild, moderate, and severe cases of 73.1%, 78.0%, and 66.1% respectively.

Normal CBC without any haematological changes was seen in 38.32%, 4%, 3.38%. There was an increasing incidence of leucocytosis, high NLR, high ANC, and lymphopenia when compared between mild, moderate, and severe groups (Table 2).

On comparing the haematological parameters between mild-to-moderate and mild-to-severe groups, there was statistical significance(P<0.05) for all the parameters except for platelet count. Whereas, haematological parameters compared between moderate and severe groups showed statistical significance for only NLR and ALC (Table 3,4).

Comorbid illness was seen in 23.35%, 36%, 44.06% of mild, moderate, and severe groups. Comorbid conditions were predominantly hypertension, diabetes followed by asthma. The severe group with comorbid conditions showed more changes in haematological parameters when compared to mild and moderate groups.

DISCUSSION

In mild COVID-19 infected patients peak age of presentation was at 31-45 years (32.9%). In moderate and severe patients, the peak age of presentation was seen in older patients i.e., 46-60 years (40% & 47.5% respectively). The age-wise distribution of cases showed statistical significance (p<0.05). These findings were similar to the studies done by Fan BE et al[7] where median was 54years for the ICU group and 41years for the non-ICU group and Li Q et al[9] study had a median of 51.5years in the non-severe group and 64years in the severe group. The occurrence of severe COVID-19 infection in the older age population was attributed to association with co-morbidities and probably decreased immunity.

In the present study, there was a male predominance with an overall male-to-female (M: F) ratio of 2.6:1 and 2.7:1, 3.6:1, and 2:1 in mild, moderate, and severe cases respectively. This was similar to various studies conducted by Guan WJ et al[10], Zhang JJ et al[11], and Chen N et al[12]. (Table 6) Though a study done by Tiwari N et al2 in paediatric cases showed contrasting findings with female predominance. The reduced susceptibility of females to viral infections could be attributed to the protection from X-chromosome and sex hormones, which play an important role in innate and adaptive immunity.[2]

In a study done by Tiwari et al[2] from north India, they analyzed haematological parameters in 32 COVID-19 patients and found that baseline CBC findings showed mild neutrophilia, lymphopenia, eosinopenia, and mild thrombocytopenia. An increase in CBC parameters, NLR was noted in follow-up cases. Anaemia was not noted in baseline CBC. A one-time Platelet lymphocyte ratio (PLR) is not indicative of disease progression.

Our analysis revealed that at the time of admission there was normal CBC in 38.32%, 5.88%, 5% of cases in mild, moderate, and severe groups. Changes in CBC with haematological parameter alteration are noted in 61.67%, 94.6%, 96.61% cases in mild, moderate, and severe groups. This shows that there are haematological changes seen as the disease progresses and it showed an increasing trend from mild to a severe group.

The present study showed that the incidence of anaemia increased with the severity of the disease. Lippi G et al[14] stated that initial assessment and longitudinal monitoring of Hb values seems advisable in patients with the SARS-CoV-2 infection, where a progressive decrease in the haemoglobin concentration may reflect a worse clinical progression.

Table 1: Age-wise distribution of patients according to COVID groups

Age	COVID Groups			Total	P value
	Mild	Moderate	Severe		
<15yrs	1.8%(3)	0.0%(0)	1.7%(1)	1.4%(4)	
16-30yrs	19.8%(33)	4.0%(2)	0.0%(0)	12.7%(35)	
31-45yrs	32.9%(55)	14.0%(7)	16.9%(10)	26.1%(72)	
46-60yrs	29.9%(50)	40.0%(20)	47.5%(28)	35.5%(98)	0.000
61-75yrs	13.2%(22)	30.0%(15)	30.5%(18)	19.9%(55)	
>75yrs	2.4%(4)	12.0%(6)	3.4%(2)	4.3%(12)	
Total	100.0%(167)	100.0%(50)	100.0%(59)	100.0%(276)	

Table 2: Haematological parameters in COVID groups

Parameters	Mild % (n)	Moderarte % (n)	Severe% (n)
Normal CBC	38.32(64)	4 (2)	3.38 (2)
Abnormal CBC	61.67(103)	96(48)	96.61(57)
Normal TLC	80.83(135)	68 (34)	55.93 (33)
Leucocytosis	7.18(12)	30 (15)	42.37 (25)
Leucopenia	11.97(20)	2(1)	1.69 (1)
Normal Hb	89.82(150)	76 (38)	74.57 (44)
Low Hb	10.17(17)	24 (12)	25.42 (15)
High N/L ratio	21.55 (36)	76 (38)	88.13 (52)
ANC- Normal	62.27 (104)	48 (24)	40.67 (24)
ANC-High	13.17 (22)	52(26)	59.32 (35)
ANC-Low	24 (41)	-	-
ALC-Low	10.17 (17)	36 (18)	57.62 (34)
Mildly low	4.19 (7)	14(7)	20.33 (12)
Moderately low	3.59 (6)	16(8)	16.94(10)
Severely low	2.39 (4)	6(3)	20.33(12)
Normal Platelet count	83.23 (139)	78(39)	83.05(49)
Thrombocytopenia	16.76 (28)	22(11)	16.94(10)

They also suggested that studies should be urgently planned to assess whether transfusion support may be helpful in this clinical setting to prevent evolution into severe disease and death. Hence, we state that low haemoglobin in COVID-19 patients may be a pre-existing finding or due to suppressive effect on haematopoietic system and its association may increase the severity, this needs to be further elucidated.

The TLC showed an increasing trend from mild, moderate to severe groups. Guan WJ et al[10] showed that leucopenia was associated with a severe disease which was in contrast to the findings in our study and the studies done by Violetis OA et al[15] and Lippi G et al.[14] A high leucocyte count was common in critically ill patients because damaged cells induce innate inflammation in the lungs which was largely mediated by pro-inflammatory macrophages and granulocytes.[16] Zaho K et al[17] stated that the patients with increased leukocyte count were significantly older (p<0.01), were more likely to have underlying chronic diseases, critical illness, admitted to an ICU, to receive mechanical ventilation and a higher rate of death.

The ANC in mild, moderate, and severe disease showed median ANC as 3640, 5526, and 7482 cells/ mm^3 respectively and found an increasing trend with statistical significance. ANC was high i.e>7000/ mm^3 in 13.17%, 52.99%, and 58.33% of cases in mild, moderate, and severe groups. This shows that as the severity of COVID-19 increases there was an increase in ANC. These findings were in concordance with studies done by Tiwari N et al[2] and Violetis OA et al[15] where they showed that there was an increase in ANC in COVID-19 patients. Kong M et al[13] showed in his study that WBC and neutrophil counts were significantly higher in the severe group than in the mild group (p 0.002 and p 0.001) whereas the ALC was significantly lower in the severe group than in the mild group(p 0.001). No significant differences in monocyte, haemoglobin, and platelet count were found. Neutrophilia is an expression of the cytokine storm, hyperinflammatory state, or superimposed bacterial infection which have an important pathogenetic role in COVID-19 and related infections such as SARS.[18]

Considering NLR in the present study, there was an increasing trend in mild, moderate, and severe COVID-19

Table 3: Comparison of haematological parameters between COVID groups

CBC	Severity	Median	IQR	P-Value
Hb	Mild	13.7	2.9	0.001*
	Moderate	12.5	2.62	
	Severe	12.4	2.3	
TC	Mild	6100	3500	0.00*
	Moderate	9700	5100	
	Severe	10100	6500	
N/L	Mild	1.94	3.61	0.00*
	Moderate	3.95	6.48	
	Severe	5.5	8.77	
ANC	Mild	3640	4256	0.00*
	Moderate	5526	4519	
	Severe	7482	4647	
ALC	Mild	1953	1248	0.00*
	Moderate	1265	966	
	Severe	968	1000	
PLT	Mild	2.16	1.1	0.83
	Moderate	1.99	1.24	
	Severe	2.23	1.52	

significant (Chi square test)

Table 4: Comparison of haematological parameters in COVID groups

		HB	TC	N/L	ANC	ALC	PLT
Mild v/s Moderate	U value	3060.000	1948.500	1190.500	1394.500	2308.000	4005.500
	p value	.004*	.000*	.000*	.000*	.000*	.663
Mild v/s Severe	U value	3588.5	1883.5	990.5	1342.5	1913.0	4775.0
	p value	.002*	.000*	.000*	.000*	.000*	.726
Moderate v/s Severe	U value	1381.0	1318.5	980.5	1241.0	1056.0	1384.0
	p value	.567	.341	.004*	.207	.016*	.580

p-value set significant at 0.05/3=0.016 (Post Hoc Man Whitney test)

Table 6: Comparison of parameters in various studies

Parameters	Fan BE et al[8] Non-ICU / ICU		Guan et al[10] Non-severe/severe		Kong et al[13] Mild /severe		Present study Mild/moderate/severe		
Age (yrs)	41 p 0.02	54	45	52	53.2 p<0.001	67	45	60	57
Sex (Male female)	53.5% 48.6% p 0.72	66.7% 33.3%	59% 41.8%	58% 42.8%	48.0% 52.0%	51.7% 48.3%	73.1% 26.9%	78% 22%	66.1% 33.9%
Hb (g%) median	14.2 p 0.07	13.2	13.5	12.8	12.8 p 0.200	12.2	13.7 p0.001	12.5	12.4
TLC (mm³) median	4700 p 0.87	5100	4900	3700	5300 p<0.002	6100	6100 p 0.00	9700	10100
ANC (mm³)	2600 p 0.17	4200	-		3100 p<0.001	4300	3640 p 0.00	5526	7482
ALC (mm³)	1300 p 0.0002	500	1000	800	1200 p<0.001	800	1953 p 0.00	1265	968
N/L ratio	-		-		3.3 p<0.001	6.6	1.94 p 0.00	3.95	5.5
Platelet (lakh/ mm³)	2.17 p 0.81	2.01	1.72	1.37	2.03 p 0.642	1.88	2.16 p 0.83	1.99	2.23

infected cases which was statistically significant. Thus, increased NLR can be used as an early predicting factor for critical or severe illness. These findings were similar to the studies done by Lippi G et al[14] and Liu J et al[6] who mentioned that patients with age >/=50 years and NLR>/=3.13 have a high risk of developing a critical illness and they should have access to an intensive care unit. MuLBSTA score incorporates six factors: Multilobe infiltrate (yes +5points), Absolute lymphocyte count <.8x10^9 (yes +4 points), Bacterial coinfection (yes +4points), Smoking history (active smoker +3, prior smoker+2), History of hypertension (yes +2), age >60yrs (yes +2). Mortality is 0.47 to 2.17% for 0-5 points, 2.92 to 9.33% for 6-10 points, 12.27 to 32.36% for 11-15 points, 39.42 to 68.99% for 16-20 points. When Liu J et al[6] compared NLR with MuLBSTA scoring model, and NLR showed higher sensitivity and specificity in predicting mortality in COVID-19 patients and was an easy-to-use predictor index.

Our study reveals that as the COVID-19 progresses there was a decrease in ALC and more reduction was seen in severe cases. This finding was in concordance with the studies done by Guan WJ et al[10] andVioletis OA et al[15] which showed lymphopenia in their studies. Fan BE et al[7] showed that between the ICU (n = 9) and non-ICU (n = 58) patients using Fisher's exact tests, they found that admission ALC stood out as discriminating laboratory indices with a p-value of <0.001. ICU patients generally had more profound lymphopenia, 7 out of 9 were lymphopenic and 4 of them were severely lymphopenic. Arentz M et al[19] studied 21 COVID-19 patients admitted in ICU and found the mean ALC of 889/ mm^3 and stated lymphopenia was one of the characteristic features in critically ill COVID-19 patients.

The mechanism of significant lymphocyte reduction in severe COVID-19 remains unclear, there is hypothesis like lymphocyte infiltration and sequestration in lungs, gastrointestinal tracts, and/or lymphoid tissue or lymphocyte express the ACE2 receptor and maybe direct target of SARS-CoV-2 infection and viral particle-induced cytoplasmic damage and apoptosis or an increase of pro-inflammatory cytokines in especially IL-6 could induce further lymphocyte reduction.[20]

Thrombocytopenia was seen in 16.67%, 21.56%, 16.66% in mild, moderate, and severe groups. On comparing the median of platelet count in mild, moderate, and severe groups, it did not show statistical significance. But it shows that thrombocytopenia exists in 16-21% of COVID-19 patients. Fan BE et al[7] showed in their study that most patients had normal platelet counts, with 20.0% having mild thrombocytopenia (platelet count100-150×10^9/L). Violetis et al[15] stated that thrombocytopenia was common in critically ill patients and usually suggests serious organ malfunction, however, needs further research. Various mechanisms like apoptosis of hematopoietic stem cells and stromal cells in bone marrow, secondary haemophagocytic mechanism of hematopoietic progenitor cells, and autoimmune destruction of platelets in reticuloendothelial systems have been hypothesised.[21]

Comorbid illness was found in 23.35%, 36%, 44.06% in mild, moderate, and severe cases respectively. Comorbid conditions were mainly hypertension, diabetes mellitus, asthma followed by ischemic heart disease and hypothyroidism. When compared to patients with no comorbid illness these patients showed an increased incidence of high N/L ratio, high ANC, low ALC. Sun Y et al[22] showed that the incidence of increased WBCs and neutrophils was higher in the Type 2 diabetes group compared to the non diabetes group (WBCs, 15.00% vs. 0.00%, P = 0:03; neutrophils, 25.00% vs. 5.00%, P = 0:01). Despite this, most cases of increased WBCs and neutrophils did not involve secondary bacterial infection. Data indicate that COVID-19 patients comorbid with diabetes have a higher risk of developing into severe cases and furthermore into critically ill cases.

Laboratory abnormalities, particularly haematological changes allow checking the status of SARS-CoV-2 infection since the hematopoietic system and haemostasis suffer significant impacts during the evolution of COVID-19. The most common haematological findings include lymphocytopenia, neutrophilia, high NLR, mild thrombocytopenia, and no evidence of monocytosis and eosinopenia. The leukocyte count may be normal, reduced, or increased.

CONCLUSIONS

COVID-19 infection was commonly seen in the middle-aged population with later age group involved in severe cases. In severe COVID-19 patients, there was increasing TLC, ANC, NLR, and lymphopenia. High NLR and low ALC are valuable early risk stratification parameters that are cost-effective and available in remote regions alleviating a shortage of medical resources and reducing mortality of critical patients during a pandemic in countries like India.

Acknowledgments

Conflict of interest: None

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