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Original Research Article

TO EVALUATE THE HEMATOLOGICAL PROFILE IN COVID 19 PATIENTS IN A TERTIARY CARE HOSPITAL IN NORTH–EASTERN INDIA

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Abstract

Background: Severe acute respiratory syndrome (SARS) caused by the new corona virus infection have been classified by The World Health Organization (WHO) to be a global pandemic resulting worldwide morbidity and mortality. Since its initial outbreak in Wuhan, China in December 2019, the virus has afflicted over one million individuals globally. SARS-CoV-2 infection will manifest as a systemic disease with the involvement of multiple organ systems including gastrointestinal, neurological, immunological, cardiovascular, and hematopoietic systems. The study aims to evaluate the hematological parameters among COVID-19 patients in a tertiary care centre in Northeast India. **Materials and Methods:** A tertiary care based cross-sectional study was conducted among COVID-19 positive patients above 18 years age during January 2021 to October 2022 at Regional Institute of Medical Sciences, RIMS, Imphal. All hematological parameters including complete hemogram, prothrombin time, erythrocyte sedimentation rate (ESR), serum lactate dehydrogenase(LDH) and D-dimer were recorded in a predesigned proforma and data were analyzed using SPSS 21. Descriptive statistics were applied. **Result:** A total of 165 COVID-19 cases were included in the study with the mean age of 50.65 (±15.79) years and majority males 89 (53.94%). Most of the hematological parameters were deranged. The present study shows leucocytosis in 70 patients (42.4%) and neutrophilia was present in all patients (165). Majority of the study subjects had lymphocytosis (147,89.9%) ,high monocyte count (159,96.36%), normal eosinophil count (93,56.36%), normal basophil count (160,96.97%),normal RBC count (135,81.82%) and normal platelet count (120,72.73%) while thrombocytopenia was noticed in 10 patients only (6.06%).Most of the participants had elevated ESR (108,65.45%),normal PT (150,90.91%), normal INR (81,49.09%) and D–dimer was high in 71 subjects (43.04%).High serum LDH was found in majority patients (98,59.39%).**Conclusion:**Study concluded that almost all the hematological parameters were elevated in Covid-19 disease however, basophil count was not altered. Platelet count and prothrombin time were elevated in 1/5th and 1/10th of the patients respectively. Both D-Dimer and LDH were elevated in half of the patients suffering from Covid-19 disease. As pandemic is going on, early clinical knowledge and hematological parameters in COVID-19 disease will guide in the management and better outcome including reduction in severity at the earliest.

INTRODUCTION

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) causing corona virus disease 2019 (COVID19) has emerged on 8th December 2019, when several cases of an acute respiratory illness-caused by an unknown, at that time pathogen- were reported in the Chinese city of Wuhan.[1] Very rapidly the infectious cause was defined and the pathogen isolated on 7th January 2020 as a novel

virus named '2019 novel corona virus' (2019-nCoV) or 'severe acute respiratory syndrome corona virus 2' (SARS-CoV-2).2SARS-CoV-2 was then renamed as corona virus disease 2019 (COVID-19) by World Health Organization (WHO) and by 11th March 2020 was declared a global pandemic.[2,3] The virus has since emerged as the cause of a devastating global pandemic with over 600 million patients affected at the time of the study period and has been responsible for more than 6 million deaths as of 2nd September 2022.[4]In India, SARS-CoV-2 has affected over 44 million patients and responsible for more than 5,20,000 deaths as on 2nd September 2022.[5]TheSARS-CoV-2 is a single-stranded RNA virus that is highly infectious and easily transmittable from human to human.[6-8] SARS-CoV-2 invades host human cells by binding to the angiotensin converting enzyme2(ACE2) receptor.[9] It has been estimated that the median incubation period (the period from exposure to the appearance of symptoms) for COVID-19 is between 2 and 14 days.[10]

COVID-19 is the constellation of clinical symptoms caused by the SARS-CoV-2 virus which range from mild respiratory symptoms to a severe and life-threatening form of pneumonia.[11-15]COVID-19 associated critical illness, is not limited to respiratory manifestations that culminate in acute respiratory distress (ARDS). In fact, it can commonly have extra pulmonary manifestations and has become recognized as a multiorgan disease affecting most systems including respiratory, cardiovascular, renal, gastrointestinal, hematopoietic and immune system.[16-18]According to the diagnosis and treatment protocol for novel corona virus pneumonia (trial version7) published by the National Health Commission of China, there are four severity levels of COVID-19 based on the clinical manifestations: mild, moderate, severe, and critical disease. The criteria used for classification are respiratory factors such as respiratory rate, oxygen saturation and lesion progression in pulmonary imaging.[19]

Early clinical knowledge of infected individuals at risk of developing complications could help reduce mortality and improve diagnosis and outcome. One of the best ways of doing this is to identify those blood parameters that have been shown through research to have good predictive value and timely monitor their levels in infected/hospitalized person. Not many significant studies have been conducted in India on hematological profile in COVID-19 patients more so in the context of state of Manipur. Keeping the deficiency of research as well as the benefit from knowing the hematological complications in COVID-19 patients in mind this study aims at comprehensive exploration on the hematological complications of the SARS-CoV-2 virus, including lymphopenia, thrombocytopenia, and disruption in the coagulation cascade leading to laboratory abnormalities and coagulopathy and present the findings in such a way as to guide clinical decisions and risk stratification for the patients admitted in COVID Ward and COVID intensive care unit(ICU) at Regional Institute of Medical Sciences (RIMS).The study aims to study the hematological profile in COVID – 19 patient and to correlate the findings with the severity of the disease.

MATERIALS AND METHODS

A hospital based cross sectional study conducted during pandemic period of January 2021 to October 2022 among patient with COVID-19 infection confirmed by RT-PCR or TRUENAT or Rapid Antigen Test (RAT), admitted in COVID ward and COVID ICU, Regional Institute of Medical Science (RIMS), Imphal, Manipur.

Inclusion Criteria

Included all cases of COVID-19 infection confirmed by RT-PCR or TRUENAT or Rapid AntigenTest (RAT) above 18 years age giving consent for the study.

Exclusion Criteria

Participants having co-morbidities such as chronic kidney disease, chronic liver disease, hematological malignancies, coagulopathy or bleeding disorders, **p**ost COVID patients became negative either by RT-PCR or TRUENATand those not giving consent for the study were excluded.

Sample Size

A sample size of 157 was calculated with error margin of 6% at 95% confidence interval.[13] This is arrived by using the formula $\mathbf{4PQ/L^2}$ Where, P is prevalence = 83[13]Q=100-P =17, L is the absolute allowable error =6 = (4×83×17) ÷ (6×6)= 5644 ÷ 36 =156.778 **= 157**

The severity of COVID -19 disease was assessed as per treatment protocol guideline.[3,5]

Study Procedure: Predesigned proforma was used which included detailed clinical history, physical examination and investigations including complete hemogram, erythrocyte sedimentation rate (ESR), Lactate dehdrogenase (LDH), Prothrombin time(PT), international normalised ratio (INR) and D-dimer were sent.

Study Tools

Complete hemogram was done using hematology automated analyser, Mindray bc 5150 made by Mindray (China), PT, INR – by HEMOSTARXF1.0, hemostasis analyzer and D-dimer by Nephelometry.

Statistical Analysis: SPSS 21.0, for Windows and graphs were prepared in Excel, Microsoft Office 2019 for statistical analysis. Descriptive statistics for continuous variables such as age, red blood cell (RBC) count was presented as mean with standard deviation (SD), median and inter-quartile range (IQR) and range. Categorical variable, sex of the participants, were presented as frequency with proportion (n, %). Blood parameters were further classified, based on their normal range, into two or

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three categories, as low, normal and high, as required. A p value <0.05 was considered significant.

Working Definitions: Anemia is defined as Hb < 13.5g/dl in males and< 12g/dl in females

Leukocytosis WBC count> 11000/mm^3, Leucopenia is WBC count < 4000/mm^3

Thrombocytopenia is Platelet count< 150×10^3/µl: Thrombocytosis is Platelet count> 450x10^3/ µl.

Lymphocytopenia is ALC <800/ mm^3 and Lymphocytosis is ALC>4000/mm^3

Approval of Research Ethics Board and Informed Consent The study was approved by Research Ethics Board Regional Institute of Medical Sciences, Imphal (REB No: A/206/REB–Comm(SP)/RIMS/2015/703/45/2020)

RESULTS

A total of 165 covid 19 positive participants were enrolled in this study. The mean age of the study subjects was 50.65 (±15.79) years. Majority of them were males 89 (53.94%) and females were 76 (46.06%). Table 1 shows hematological pattern among COVID-19 patients. Gender wise distribution of hematological profile among COVID-19 patients was shown in table 2. The present study shows leucocytosis in 70 patients (42.4%), more in males (42, 47.19%). Neutrophilia was present in all patients (165), more in males (89,100%). Majority of the study subjects had lymphocytosis(147,89.9%) greater in males (78,87.64%).Most of them had high monocyte count (159,96.36%) more in males (86,96.63%).Maximum patients had normal eosinophil count (93,56.36%) while eosinophilia was seen in 72 patients (43.64%).Similarly, majority of the study subjects had normal basophil count (160,96.97%) and high basophil count was noticed in only 5 patients (3.03%).The mean RBC count in the present study was 4.25 (±0.77) x 1012 cells/L and maximum patients had normal RBC count (135,81.82%) and 23 patients (13.94%) had low RBC count. Mean platelet count, 4.64 (±0.9) x 109 cells/L, most of them had normal platelet count (120,72.73%) while thrombocytopenia was noticed in 10 patients only (6.06%), more in males (9,10.11%).Most of the participants had elevated ESR (108,65.45%) more common among males (66,74.16%),normal PT (150,90.91%) and normal INR (81,49.09%) while elevated PT was seen in 15 subjects (9.09%) and elevated INR in 77 patients (46.67%). D–dimer was normal in most patients (94, 56.97%) and high in 71subjects (43.04%) while majority of them (39 of 71) were male participants. High serum LDH was found in majority patients (98, 59.39%) and there was a male predilection (42 females vs 56 males of 98 individuals had higher LDH).

Table 1: Hematological parameters in COVID-19 patients (N=165)

Hematological parameter	Mean (±SD)	Median (IQR)	Range
Total Leucocyte Count (TLC) (cells/L)	11222 (±6473) x 106	9800 (6210-14750) x 106	2790 to 42980 x 106
Neutrophil Count (cells/L)	78 (±14) x 109	83 (72-88) x 109	31 to 97 x 109
Lymphocyte Count (cells/L)	16 (±8) x 109	12 (7 - 21) x 109	2 to 64 x 109
Monocyte Count (cells/L)	5 (±1.3) x 109	5 (3-7) x 109	1 to 15 x 109
Eosinophil Count(cells/L)	0.7 (±.01) x 109	0.1 (0 -1) x 109	0.1 -1 x 109
Basophil Count (cells/L)	0.3 (±0.17) x 109	-	-
Red Blood Cell Count (cells/L)	4.25 (±0.77) x 1012	4.24 (3.80-4.67) x 1012	2.1 to 7.5 x 1012
Platelet count (cells/L)	4.64 (±0.9) x 109	2.02 (1.51-2.9) x 109	0.45 to 8.8 x 109
Erythrocyte Sedimentation Rate (ESR) (mm/hr)	36.79 (±26.45)	30 (15-50)	5 to 100
Prothrombin time in seconds	12.22 (± 1.63)	12 (11-13)	10 to 17
International Normalized Ratio	1.24 (±0.25)	1.2 (1-1.4)	0.8 to 1.8
D-Dimer value (µ/mL)	0.61 (± 0.49)	0.40 (0.30-1.00)	0.2 to 2.5
Lactate Dehydrogenase (LDH) (IU)	595.94 (±253.83)	490 (400-820)	240 to 1150

*SD: Standard Deviation; IQR: Inter-Quartile Rang

Table 2: Gender wise distribution of hematological profile among COVID-19 patients (N=165)

Hematological parameter		Gender (Frequency, %)		
		Male	Female	Total
Total leucocyte count:	Low	4 (5.26%)	7 (7.87%)	11 (6.67%)
	Normal	44 (57.89%)	40 (44.94%)	84 (50.91%)
	High	28 (36.84%)	42 (47.19%)	70 (42.42%)
Neutrophil count	High	76 (100%)	89 (100%)	165 (100%)
Lymphocyte Count	Normal	7 (9.21%)	11 (12.36%)	18 (10.91%)
	High	69 (90.79%)	78 (87.64%)	147 (89.09%)
Monocyte Count	Normal	3 (3.95%)	3 (3.37%)	6 (3.64%)
	High	73 (96.05%)	86 (96.63%)	159 (96.36%)
Eosinophil Count	Normal	49 (64.47%)	44 (49.44%)	93 (56.36%)
	High	27 (35.53%)	45 (50.56%)	72 (43.64%)
Basophil Count	Normal	73 (96.05%)	87 (97.75%)	160 (96.97%)
	High	3 (3.95%)	2 (2.25%)	5 (3.03%)
Red Blood Cell Count	Low	8 (10.53%)	15 (16.85%)	23 (13.94%)
	Normal	68 (89.47%)	67 (75.28%)	135 (81.82%)
	High	0 (0.00%)	7 (7.87%)	7 (4.24%)
Platelet count	Low	1 (1.32%)	9 (10.11%)	10 (6.06%)

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	Normal High	55 (72.37%) 20 (26.32%)	65 (73.03%) 15 (16.85%)	120 (72.73%) 35 (21.21%)
Erythrocyte Sedimentation Rate	Normal High	34 (44.74%) 42 (55.26%)	23 (25.84%) 66 (74.16%)	57 (34.55%) 108 (65.45%)
Prothrombin time	Normal High	71 (93.42%) 5 (6.58%)	79 (88.76%) 10 (11.24%)	150 (90.91%) 15 (9.09%)
International Normalized Ratio	Low Normal High	4 (5.26%) 32 (42.11%) 40 (52.63%)	3 (3.37%) 49 (55.06%) 37 (41.57%)	7 (4.24%) 81 (49.09%) 77 (46.67%)
D-Dimer	Normal High	44 (57.89%) 31 (42.11%)	50 (56.18%) 39 (43.82%)	94 (56.97%) 71 (43.03%)
Lactate Dehydrogenase	Normal High	34 (44.74%) 42 (55.26%)	33 (37.08%) 56 (62.92%)	67 (40.61%) 98 (59.39%)

DISCUSSION

The hematological profiles of 165 COVID-19 patients were evaluated in the present study. Patient's age range from 21 to 80 years of age, with slightly more male patients than females. Leukopenia was evident from nearly 7% of the patients suffering from COVID, though the individual white blood cell (WBC) count was not the higher in most cases. Thrombocytopenia was evident among 6% of the COVID patients, while erythrocytopenia was evident from nearly double (14%) of patients exhibiting leukocytopenia. Erythrocyte Sedimentation Rate (ESR), LDH, INR was found to be elevated for majority of the patients. The PT was not high for (9%) of the patients while D-dimer was high in 71 subjects (43.04%).

The reduced TLC among COVID-19 infected patients have been evident from earlier researches. In the study by Huang C et al,[20] they found the prevalence of leukopenia to be around 25% (10 out of 40 patients) of their study population, which was a bit higher than this study (11,6. 67%). While Lee N et al,[21] described leukopenia in 33.9% patients, Wong RS et al,[22] in 64% patients. This discrepancy could be a result of difference in sample size and also conducted in different population. Liu X et al,[23] in their study mentioned of co-occurrence of leukopenia along with reduced lymphocyte count which is consistent with the study by Guan W et al,[13](lymphocytopenia in 83.2% of the admitted patients). However, in our study leukopenia was quite less prevalent and lymphocytopenia was not at all evident among the COVID-19 infected patients. Probable reasons behind these differences could be due to different population: varied susceptibility, individual's immunity, geographic location etc. and different time-frame: the reference studies were conducted during the very early days of COVID infection (early 2020) and this study was conducted from January 2021, till October, 2022.

Reduced thrombocytes/thrombocytopenia during COVID infection were evident among 6% of our study participants while number of thrombocytes were beyond the normal level in blood samples of more than 21% of the hospitalized patients. Chang D et al,[24] in his study outside Wuhan city of China, reported thrombocytopenia in nearly 3/4th participants. While Wool GD and Miller JL noticed thrombocytopenia ranging between 5% to 41.7% in their review. In our study, the mean platelet counts for those who accounted for low platelet group, was observed with a platelet count of 0.825 x 109 cells/liter of blood, which was lower than Wool GD and Miller JL's review.[25] They also mentioned of mild thrombocytopenia, that was found among (58-95%) of COVID infections with severe symptoms.[13,26,27] where patient's average platelet count dropped to 23-31 x 109 cells/liter.[11,28] Patients undertaking treatment for COVID-19 might require blood or platelet transfusion or plasma exchange in case of severe deficit of platelets.

Increased plasma levels of cytokines, such as interleukin (IL)-6 and tumour necrosis factor-alpha (TNF-α), are indicative of cytokine storm, which is linked to a deterioration of the clinical status in COVID-19 patients. The hematological system is also impacted by these inflammatory cytokines, leading to anomalies in peripheral smears, coagulation tests, complete blood count (CBC) values, etc.[29]

SARS CoV-2 can infiltrate lymphocytes, megakaryocytes(MKs) and hematopoietic stem/progenitor cells through ACE2, CD13, or CD66a receptors which can lead to cellular death, suppressed cell proliferation, lymphopenia and thrombocytopenia. This virus also effects the BM microenvironment, which include endothelial cells and thus weaken hematopoiesis causing hemocytopenia. The lower lymphocyte content in COVID 19 patients may also be explained by glucocorticoid-induced lymphopenia.[30]

The mean erythrocyte counts among the study populations were within the normal range. Almost 82% of the blood samples contained red blood cell (RBC) count in the normal range. However, nearly 14% of the population were diagnosed with low RBC count, which was at par with the studies by Mei Y et and Elderdery AY et al.[31,32]

Erythrocyte Sedimentation Rate (ESR), another blood parameters that indicates inflammation in the body, was found to be on the higher side for nearly two-third of the study populations which was consistent with Ghahramani S et al,[33] in his recent systematic review and meta-analysis. Pu SL et al,[34] in a case report, supported high ESR during COVID-19 infection and also mentioned that elevated ESR sustaining for more than a month, can cause negative effect on COVID-19 patients'

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prognosis. In the same study, other blood parameters, such as LDH, PT, D-dimer was also found to be elevated among patients, infected with COVID-19 virus that is in accordance to our findings. Platelet count of the COVID-19 infected patients was reduced for 6% of the study population. Probably due to that, prothrombin time was elevated not for many patients (9% experienced elevated PT). A case-series among hospitalized patients from Wuhan, China by Wang D et al,[15] reported prolonged PT among 58% of the samples which is in contrast to study done by Wu C et al,[35](2.1% patients). Having a high D-dimer level in blood can be a sign of a blood clotting disorder since the level of D-dimer can rise greatly when there's significant formation and breakdown of blood clots in human body.[36-39]

High serum LDH was found in majority patients (98, 59.39%) and there was a male predilection (42 females vs 56 males of 98 individuals had higher LDH) which was at par with the study by Ostadi F et al[40]. An essential component of cellular metabolism is the enzyme LDH, which converts lactate to pyruvate. Different tissues contain LDH, which is released into the bloodstream in reaction to injury or damage to cells. Increased LDH has been linked to inflammation, tissue damage, and unfavourable prognoses in a number of illnesses, including respiratory infections. This LDH may be helpful in predicting the severity of an illness and helping to identify those who are more likely to have unfavourable outcomes and require longer hospital stays. Therefore, monitoring LDH levels may be helpful in determining which patients are more likely to need intensive care, as well as in allocating resources and making treatment decisions.[40] One of the study conducted in India demonstrated similar findings with altered LDH and other blood markers.[41]

In COVID-19, endothelial damage initiated coagulopathy leading to the production of thrombin and the inhibition of fibrinolysis. This exacerbates the hypercoagulable state resulting in prolongation of the prothrombin time and aPTT. However in the late stages of DIC, consumptive coagulopathy occurs causing decrease in PT, aPTT, fibrinogen, and platelets, as seen in some of none survivors. Furthermore, coagulation abnormalities were more common in COVID-19 individuals with cardiac damage and increased troponin-T levels than in those without cardiac involvement.[42]

Blood parameters from the study samples helped to understand the disease outcome. Their deviation from the normal range can help estimating relation to disease severity.

Limitations

In the present study, there were several similarities and dissimilarities with other study findings, that indicates the need for wider sample size from different locations to make the study findings more generalizable. This study is not free from its limitations. First, the patients were limited to a single health care system from the capital city of Manipur state. So, there is a high chance, most of the patients were local, reducing the representativeness from the rural population. Secondly, the hospitalized patients were mostly of moderate to severe grade, number of mild diseased ones could be very less in the sample. Furthermore, this study is cross-sectional in nature, so it is not possible to establish the biological plausibility between each of the outcome and COVID-19 infection.

CONCLUSION

This study concluded that majority of hematological parameters were elevated among Covid-19 patients however, basophil count was not altered. Leucopenia, lymphocytosis, monocytosis were remarkable findings in the present study. Platelet count and prothrombin time were elevated only in 1/5th and 1/10th of the patients respectively. Both D-dimer and LDH were elevated in half of the patients suffering from Covid-19 disease. This study suggest the proper screening of hematological profile is a necessity in the treatment protocol or management line of covid -19 infected patients.

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