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ORIGINAL RESEARCH

To Investigate The Importance Of The CBC, Derived Parameters, And Morphology Of Peripheral Blood Cells In Covid-19 Patients

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Abstract
Aim: To investigate the importance of the CBC, derived parameters, and morphology of peripheral blood cells in Covid-19 patients.
Material and methods: According to their symptoms, patients were classified as asymptomatic, mild, or moderate-severe. This research included all paediatric and adult patients who had two CBC samples available (one at admission and another during discharge) throughout their hospital stay. Those who were already undergoing therapy for their cancer, haematological illness, liver disease, or chronic lung disease were not allowed to participate.
Results: Patients' ages varied from 8 to 71. The patients' average age was 36.15±14.58 years. Sixty percent of research participants were male, making up a sex ratio of 1.5:1. (M: F). The average white blood cell count was 6.87±3.51 $x10^9$/L, the average red blood cell count was 4.61±0.88 $x10^6$/microL, and the average haemoglobin level was 12.80±2.15 g/dl upon admission. The average absolute neutrophil count was 3.81±3.46$x10^9$/L, the average absolute lymphocyte count was 2.31±1.40$x10^9$/L, the average absolute monocyte count was 0.38±0.31$x10^9$/L, and the average absolute eosinophil count was 0.15±0.18$x10^9$/L. Overall, the average number of platelets per microliter of blood was 149.21± 80.25. Neutrophil to lymphocyte ratio (NLR) at admission was 3.806; platelet to lymphocyte ratio (PLR) was 116.32±13.1; lymphocyte to monocyte ratio (LMR) was 8.91±5.25, and derivative neutrophil to lymphocyte ratio (d-NLR) was 2.61±1.36. Twenty (40%) of the patients were asymptomatic at admission, while 44% had mild symptoms, and 16% required oxygen and ventilator support due to moderate to severe symptoms. The RT-PCR test was positive for all of the patients examined. There was a noteworthy shift in both the mean WBC and mean platelet counts after the follow-up evaluation. No correlation was seen between clinical state on admission and any of the other CBC measures ($p>0.05$)
Conclusion: The significance of CBC values and morphological inspection of the peripheral blood smear at baseline and subsequent assessment is highlighted in the research.
Keywords: CBC, peripheral blood cells Covid-19

Introduction

The novel coronavirus known as Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), the cause of Corona Virus Disease 19 (COVID-19), was first reported in December

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2019 in Wuhan, China, and is known to cause fatal inflammatory responses and acute lung injury.[1,2] A wide variety of symptoms, from a mild cough and myalgias to severe breathlessness due to pneumonia and ARDS, are experienced by patients with COVID-19. Other systemic manifestations include central nervous system involvement, a coagulopathy associated with COVID-19 that mimics disseminated intravascular coagulopathy, anosmia, ageneusia, autoimmune hypersensitivity reactions, and severe diarrhoea with nausea. In addition, a condition known as COVID-19 great toe has been observed in a subset of young people. This is the benchmark for evaluations. As COVID-19 patients progress through their illnesses, a variety of diagnostic tools, including RT-PCR (Real-time reverse transcriptase-polymerase chain reaction), imaging studies, and laboratory analyses, are used to determine the disease's origin. HRCT (high resolution computed tomography) and chest x-ray is a common diagnostic tool because of how helpful it is in patient monitoring. The complete blood count (CBC) and its derivatives, the neutrophil lymphocyte ratio (NLR), the platelet lymphocyte ratio (PLR), the lymphocyte monocyte ratio (LMR), and the derived neutrophil lymphocyte ratio (dNLR), are important investigative tools that provide an insight into the severity of inflammation, which can predict further clinical course and the associated systemic complications and, thus, help the clinician assess the clinical status, disease progression, and plan the treatment.[3,4] CBC and its derived parameters are routinely being done in the laboratories, but the importance of peripheral blood smear examination to study the alteration in blood cell morphology in COVID-19, has been overlooked until now. So far, only a small number of articles have been published that specifically address the morphological features of the peripheral blood smear in COVID-19. After extensive search on the Google database, we found few studies discussing the morphological findings in the peripheral smears.[5,6]A study of 15 cases documented normocytic normochromic changes in the majority of the cases, and hemolysis was not observed in any case.[7] The study also mentioned the presence of medium to large size atypical lymphocytes having loosely condensed chromatin with moderate to deep basophilic cytoplasm. Some unusual cells with plasmacytoid morphology with eccentric nuclei, perinuclearhoff and some imitating immunoblasts were also found in the research. They also compared the smear's lymphocyte population to the clinical finding at the time of collection and discovered that the number of atypical lymphocytes was unrelated to disease severity. Leukocytosis with neutrophilia, relative lymphocytopenia, and monocytopenia have all been found on initial complete blood count (CBC) and peripheral blood cell morphology tests of COVID-19 patients, with the monocyte count improving from day 5 onwards. Flowcytometric analysis has also been studied in a small number of these studies for its potential in detecting changes in the monocyte subpopulation due to COVID.[4,6 ,8,9] There is a clear need for research in this area, particularly in the Indian context, as there is currently no study correlating the peripheral blood morphological findings, complete blood count, and its derivatives, with the clinical course of the disease at two different points in time, in COVID-19.

Material and methods

Ethical approval was obtained for this investigation, which was conducted in the department of Pathology. According to their symptoms, patients were classified as asymptomatic, mild, or moderate-severe. This research included all paediatric and adult patients who had two CBC samples available (one at admission and another during discharge) throughout their hospital stay. Those who were already undergoing therapy for their cancer, haematological illness, liver disease, or chronic lung disease were not allowed to participate. Excluded were those patients for whom a subsequent CBC sample could not be obtained.

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Methodology

The demographic data, the clinical status of the patients at the time of admission and at follow up during the hospital stay (duration for which the follow-up samples were considered ranged from 7-10 days) and haematological findings (Complete blood counts and peripheral blood smear examination for cell morphology) were recorded at admission and at follow up. Fifty patients met all of the study's inclusion criteria and were included in the analysis. The patients were categorised on the basis of their clinical presentation on the day of admission as asymptomatic (n=20), moderately symptomatic (n=22), and moderate to severely symptomatic (n=8). The samples were run through a 5-part haematology analyzer (Abbott Cell Dyn Ruby) to get a full blood count, and Romanowsky stains were used to examine smears of peripheral blood. On the day of admission and the day of the repeat sample, the results and morphological changes of the peripheral blood smear were recorded, as were the values and alterations in the CBC parameters and its derived parameters. Between 7 and 10 days was allotted for further contact. Findings were connected with patients' actual health conditions. One of three possible outcomes—improvement, stability, or worsening—was used to determine the success of the study. The data was analysed using SPSS 22.0 (Statistical Package for the Social Sciences). Data comparisons were performed using the Chi-square test, the paired t-test, and the analysis of variance. Significant correlations were shown by p-values less than 0.05.

Results

Patients' ages varied from 8 to 71. The patients' average age was 36.15±14.58 years. Sixty percent of research participants were male, making up a sex ratio of 1.5:1. (M: F). The average white blood cell count was 6.87±3.51 $x10^9$/L, the average red blood cell count was 4.61±0.88 $x10^6$/microL, and the average haemoglobin level was 12.80±2.15 g/dl upon admission. The average absolute neutrophil count was 3.81±3.46$x10^9$/L, the average absolute lymphocyte count was 2.31±1.40$x10^9$/L, the average absolute monocyte count was 0.38±0.31$x10^9$/L, and the average absolute eosinophil count was 0.15±0.18$x10^9$/L. Overall, the average number of platelets per microliter of blood was 149.21± 80.25. Neutrophil to lymphocyte ratio (NLR) at admission was 3.80; platelet to lymphocyte ratio (PLR) was 116.32±13.1; lymphocyte to monocyte ratio (LMR) was 8.91±5.25, and derivative neutrophil to lymphocyte ratio (d-NLR) was 2.61±1.36 (Table 1). Twenty (40%) of the patients were asymptomatic at admission, while 44% had mild symptoms, and 16% required oxygen and ventilator support due to moderate to severe symptoms. The RT-PCR test was positive for all of the patients examined. There was a noteworthy shift in both the mean WBC and mean platelet counts after the follow-up evaluation. The mean white blood cell count rose from 6.87±3.15 to 8.31±4.25 (1.44±1.10 increase; p=0.021) during the course of the study. The platelet count rose from 149.21±80.25 to 199.87±77.85, an increase of 50.66±2.40 (p=0.002), indicating statistical significance. Parameters related to the CBC have not changed much. (Table 1). Two (4%) of the patients tested positive for the virus using RT-PCR throughout the follow-up period, indicating a 94% decrease in the positivity rate (p0.001). Only haemoglobin levels were significantly correlated with the patients' clinical state on admission when examining the CBC values. The tendency for lymphocyte counts to decrease from the asymptomatic to the moderate-severely symptomatic group was marginally non-significant (p=0.055). No correlation was seen between clinical state on admission and any of the other CBC measures (p>0.05) (Table 2). In addition, we found that most patients (78%) were clinically recovered (scheduled for release) with negative RTPCR at the time of the repeat sample, while four patients (14%) were recovering with negative follow-up RTPCR and only four instances (8%) were in the intensive care unit (ICU) but stable. Two of the four patients in the intensive care unit had negative RT-PCR results after follow-up, whereas the other two

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had persistently positive results. The white blood cell count, absolute neutrophil count, absolute monocyte count, platelet count, and their derivatives NLR, PLR, and d-NLR all varied significantly among individuals with various clinical statuses.

Clinically healed patients (scheduled for release) had a substantially lower mean WBC count (6.75±3.58) compared to those in the intensive care unit (13.80±2.24) or those in recovery (13.51±3.52). Both absolute neutrophil and monocyte counts followed a similar pattern. Patients that were stable (undergoing ICU treatment), recovering, and clinically recovered (scheduled for release) all had platelet counts that were highest. Patients who were stable (receiving ICU care) had the lowest NLR, followed by those who were recovering (the highest), and finally those who were clinically recovered (the lowest). PLR was highest for stable cases (those in intensive care) and lowest for recovered cases (those who were scheduled for release). At the same time, d-NLR was highest in the ICU, lowest in the group of patients who were deemed ready for release (recovering patients), and lowest in the group of patients (Table 3)

Table 1: Clinico-hematological profile of patients at admission and at follow-up

	Mean+SD	**Mean+SD**	**P value**
Male: Female	30 (60%) : 20 (40%)		
Mean Age±SD	36.15 ± 14.58		
RBC (10^6/mm^3)	4.61±0.88	4.69±0.80	0.55
Hb (gm/dl)	12.80±2.15	12.68±2.30	0.61
WBC (10^3/microL)	6.87±3.15	8.31±4.25	0.041
Neutrophil (10^3/microL)	3.81±3.46	5.20±3.82	0.063
Lymphocyte (10^3/microL)	2.31±1.40	2.47±1.17	0.57
Monocyte (10^3/microL)	0.38±0.31	0.49±0.37	0.22
Eosinophil (10^3/microL)	0.15±0.08	0.17±0.09	0.41
Platelet(10^3/microL)	149.21±80.25	199.87±77.85	0.003
NLR	3.80±1.96	2.99±1.12	0.45
PLR	116.32±13.1	99.86±61.44	0.63
LMR	8.91±5.25	36.98±15.85	0.25
d-NLR	2.61±1.36	1.94±1.11	0.39
RT-PCR Positive	50	2(4%)	
At admission status			
Asymptomatic Mildly	20(40%)		
Symptomatic	22(44%)		
Mod to Severe	8(16%)		

Table 2: Association of CBC parameters with Clinical Status at admission

	Asymptomatic (n=20)	**Symptomatic (n=22)**	**Mod/Severe Symptomatic (n=8)**	
	Mean+SD	**Mean+SD**	**Mean+SD**	**P value**
RBC (10^6/mm^3)	4.27±1.33	4.77±0.87	4.61±0.63	0.21
Hb (gm/dl)	11.45±1.63	14.04±1.54	12.46±2.58	0.007
WBC (10^3/microL)	7.54±4.55	6.47±2.47	6.11±2.87	0.58
Neutrophil(10^3/microL)	3.87±2.39	3.89±1.57	4.24±2.57	0.63
Lymphocyte(10^3/microL)	2.86±0.69	1.98±0.87	1.23±0.87	0.055
Monocyte(10^3/microL)	0.46±0.33	0.38±0.12	0.31±0.44	0.36
Eosinophil(10^3/microL)	0.22±0.11	0.11±0.01	0.01±0.001	0.074
Platelet(10^3/microL)	159.14±41.67	158.62±59.87	115.56±45.69	0.56
NLR	1.85±0.54	4.05±2.25	7.68±4.85	0.47

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PLR	70.58±33.67	150.92±111.25	128.69±57.61	0.52
LMR	14.83±6.55	5.61±2.87	4.17±1.66	0.25
d-NLR	1.91±1.87	2.30±3.67	4.58±2.58	0.63

Table 3: Association of CBC parameters with Clinical Status at follow-up

	ICU but Stable (n=3)	**Recovering (n=5)**	**Recovered (Planned for Discharged (n=45)**	**P value**
	Mean+SD	Mean+SD	Mean+SD	
RBC(10^6/microL)	4.70±0.36	4.62±1.63	4.70±0.81	0.85
Hb (gm/dl)	12.35±1.63	11.98±2.69	12.86±1.87	0.44
WBC(10^3/microL)	13.80±2.24	13.51±3.52	6.75±1.74	<0.001
Neutrophil(10^3/microL)	9.90±2.69	10.95±4.85	3.58±1.52	<0.001
Lymphocyte(10^3/microL)	2.30±1.22	1.59±0.21	2.66±1.11	0.22
Monocyte(10^3/microL)	1.13±0.31	0.89±0.12	0.36±0.31	<0.001
Eosinophil(10^3/microL)	0.04±0.01	0.16±0.11	0.18±0.11	0.587
Platelet(10^3/microL)	352.00±98.58	188.00±80.74	191.57±50.84	0.036
NLR	5.45±2.67	7.92±3.74	1.76±1.03	<0.001
PLR	181.38±57.84	141.20±68.74	85.02±44.78	0.021
LMR	2.26±0.04	2.11±1.44	48.33±11.87	0.53
d-NLR	3.33±2.87	4.31±1.74	1.33±0.69	<0.001

Discussion

Many studies have been conducted since the global COVID-19 pandemic began to learn more about the virus's origin, pathophysiology, clinical course, and progression, and to identify a viable antiviral medication and vaccine. Once believed to just affect the lungs, COVID-19 is now recognised as a multi-system illness that may affect any or all of the body's organs and tissues.[10,11] However, investigations have demonstrated that the virus induces changes in peripheral blood leukocyte and lymphocyte counts, resulting in normal to low count, throughout the incubation period and the early stage of the disease.[4-6] The lungs, heart, and intestines are particularly vulnerable because viremia in the illness concentrates in these organs.[12] A "cytokine storm" developed in some individuals with severe symptoms because of the increased systemic inflammatory response. Several research have looked at how COVID-19 infection affects the complete blood count (CBC) and its associated parameters, but very few have looked at the Indian population, where the pandemic is spreading at an alarming rate.[13,14]From an Indian point of view, we've published a research correlating CBC results with the patient's clinical presentation and eventual fate in 32 COVID-19 instances.[14] Mild symptoms were reported in paediatric patients. A complete blood test taken at the start of the study revealed moderate neutrophilia, lymphopenia, eosinopenia, and a normal to slightly elevated platelet count. A higher NLR was also detected in certain patients via hospital follow-up tests. Lymphocytopenia was the most common cytopenia at presentation (83.2%), followed by thrombocytopenia (36.2%) and leukopenia (33.7%), according to one study.[15] They also found a correlation between the results and clinical condition, observing that peripheral blood abnormalities were more common in severe instances than in non-severe cases (96.1% vs. 80.4% for lymphocytopenia, 57.7% vs. 31.6% for thrombocytopenia, and 61.1% vs. 28.1% for leucopenia).[16] Few other descriptive investigations undertaken at the same time in China and included a total of 41, 99, 138, and 201 confirmed cases of COVID-19 reached similar conclusions. Many studies have linked low lymphocyte counts to the requirement for intensive care unit (ICU) admission; for example, Wu et al. demonstrated a connection between lymphopenia and the onset of acute respiratory distress syndrome (ARDS).[15-18] Among 201 patients with COVID-19 pneumonia

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in Wuhan, China, Wu et al. conducted a retrospective analysis of potential risk factors for the development of ARDS and death.[16] Neutrophils, regulatory T-cells that promote early hyperactivation followed by fast depletion of cytotoxic CD8+ T-cells, were substantially related with an elevated risk of ARDS along the course of the disease.[19] Fan et al. observed similar results in their research of Singaporean patients who needed intensive care unit involvement; these patients had considerably lower lymphocyte counts.[20] Most patients (78%) in the present research were clinically recovered (scheduled for release) with negative RTPCR, four patients (14%) were recovering with negative follow-up RTPCR, and four cases (8%) were in the intensive care unit but stable. Two of the four patients in the intensive care unit had negative RT-PCR results after follow-up, whereas the other two had persistently positive results. There were statistically significant variations in white blood cell count, absolute neutrophil count, absolute monocyte count, platelet count, and derivatives like NLR, PLR, and d-NLR amongst individuals of varying clinical statuses. COVID-19 causes changes in the morphology of cells in the peripheral blood, as shown by a small number of research published in China and Italy.[4,6] Changes in the morphology and function of monocytes and macrophages were observed using wright stained smears and flow cytometry in a study of 28 patients with confirmed COVID-19 infection of varying severity; these changes were found to be predictive of disease severity, likelihood of ICU admission, length of hospital stay, and full recovery.[4] A small number of Indian studies have described different morphological changes in red blood cells (RBCs), white blood cells (WBCs), and platelets, but none have examined whether or not these changes have any clinical significance at the time of diagnosis or during the course of the patient's disease.[5,21] Our goal in this research was to demonstrate the relevance of examining peripheral smear cell morphology in addition to CBC parameters and to show how this information correlates clinically with the patient's state on the day of arrival and as the illness progresses. The correlation between CBC parameters, smear morphology, and clinical-molecular profile supports the utility of peripheral blood smear examination as an ancillary tool for the pathologist, which may indicate the presence of virus-induced changes in the non-infectious or asymptomatic stage of the disease before the RT-PCR results are available.

Several morphological alterations, most notably in the WBC series and in platelets, were detected upon examination of peripheral blood cells as a result of this condition. The most striking observation was of big, unusual cells with basophilic cytoplasm, perhaps a virocyte mislabeled as a "covicyte," albeit all WBCs had minor alterations. We found that three patients with significant clinical symptoms and the need for respiratory assistance had lasting alterations in all three cell lineages throughout a follow-up period of 7-10 days. In a research by Singh et al. the authors noted that the morphological anomalies in peripheral smear comprised numerous packed, black granules in the cytoplasm of polymorphs (similar to “toxic” granules) and of peripheral light blue agranular region. Sometimes polymorphs showed hypogranularity in the cytoplasm. Abnormalities of nuclear shape were apparent, with higher frequency of band formations and dyspoeitic characteristics, with entire lack of nuclear segmentation, corresponding with pseudo-PelgerHeutabnormalities.[5] Apoptotic cells were readily identified in several peripheral blood films and they appeared with liquefied nuclear chromatin and granular or deep blue cytoplasm, indicating likely origin from distinct kinds of cells (i.e., neutrophils and lymphocytes, respectively). Immature granulocytes, notably tiny myelocytes and metamyelocytes, occasionally revealing immature nuclei and small azurophilic granules, were found. However, when evaluating the smears following treatment, the authors found a decrease of modifications in the polymorphs but permanent changes in the lymphoid cells.[6] In the Indian scenario two studies, one case report of a 55 year old female with respiratory symptoms and positive RT-PCR and one short commentary published by the authors explained the morphological findings in peripheral smear of

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COVID- 19 cases which include RBC with mainly non-specific changes, neutrophils with toxic granules, vacuoles, hypolobation, dyspoiesis, lymphocyte with lymphocytopenia, large granular lymphocyte, variant reactive monocytoid and plasmacytoid forms and blastoidforms, monocytes with large bizarre forms, vacuoles, granules, platelets with agglutination and thrombocytopenia.[5,21] Changes generated by viruses are known to be long-lasting and to fade slowly, particularly in the lymphoid cell population. The research showed that in all of these instances, the RBC abnormalities were still present in the subsequent CBC, whereas the WBC results were varied on follow-up. Nonetheless, in three cases needing ongoing ICU care, changes in lymphoid and monocytoid cells were still present. Therefore, it is possible to hypothesise that the persistence of a severe post-COPD I virus infection prodrome, or the occurrence of a re-infection of COVID, is due to the persistence of viral genome in the infected cells and, that these morphological changes are not merely a byproduct of cytokine storm, but rather, danger signs in patients where they persist, alerting the clinicians to closely follow up these recovered patients. Moreover, as shown by Zhang et alinvestigations of a monocyte subset, it is clear that the peripheral smear in no other viral infection is similar to that of COVID-19. Our results corroborate those of a previous research that also found evidence of lympho-plasmacytoid cells in peripheral smear cells after analysing COVID-19 morphology. In the instances we analysed, plasmacytoid cells were also present. Another important result was the discovery of apoptotic cells at the periphery of the smear.[22]

Conclusion

The significance of CBC values and morphological inspection of the peripheral blood smear at baseline and subsequent assessment is highlighted in the research. Our findings reveal that in a significant proportion of individuals with moderate to severe symptoms, abnormal monocytoid cells persisted or were present (covicytes). The results suggest that the severity of post-COVID syndrome may be predicted by closely monitoring CBC values in conjunction with peripheral blood cell morphology.

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