International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Screening of Peripheral Blood Film for Abnormalities in Leucocyte Morphology in Mild to Moderate COVID-19: A Promising Screening Tool for Guiding Quick Clinical Diagnosis in Outpatient Clinics

Dr. Maitrayee Roy[1], Dr. Akshay Bali[2]

[1]MD FRCPath
[2]MD DipRCPath

Running title: Abnormal leucocyte morphology in mild to moderate COVID-19

Corresponding author: Dr. Akshay Bali MD, DipRCpath, Consultant Pathologist, Maitri Diagnostic Lab, Ambala City, Haryana, India

Abstract: ***Objective: Abnormal leucocyte count, namely neutrophilia, lymphopenia and even eosinopenia is well documented in COVID-19 patients. But the morphological changes in leucocytesare chronicled in few studies and mostly in hospitalized cases. We endeavored to study the morphological changes in neutrophils, lymphocytes and monocytes in confirmed COVID-19 cases with mild to moderate symptoms as well as asymptomatic contacts presenting at an outpatient clinic. Material and methods: The study included 36 COVID-19 diagnosed cases, including 30 patients with mild to moderate symptoms and six asymptomatic contacts, presenting at an outpatient clinic. The venous blood samples collected at presentation were run on three-part hematology analyzer and peripheral blood films were examined by a pathologist for morphological abnormalities in WBCs. Results: The total leucocyte count was within normal reference range in all except one patient. Although neutrophilia and lymphopenia were evident in 25% of cases, PBF examination revealed constellation of morphological changes in leucocytes in all cases, including asymptomatic contacts. Nuclear spikes (80%), abnormal nuclear shapes and segmentation (75%) in neutrophils were frequently observed. Howell-Jolly body like inclusion in neutrophils was a noteworthy finding in one-third patients. Reactive/ plasmacytoid lymphocytes and abnormal coalescent cytoplasmic vacuoles in monocytes were observed in nearly half of our patients. Conclusion: COVID-19 induces a wide range of quantitative and qualitative changes in both granulocytes and agranulocytes, even in patients with mild symptoms and asymptomatic contacts.***

Key words: COVID-19, mild symptoms, leucocytes, morphology

1. Introduction

Umpteenth number of novel viruses have created epidemics between 2001 and 2019, notably SARS-COV in 2002, H1N1 in 2009 and MERS-COV in 2012. The latest epidemic to hit humanity is attributed to a novel coronavirus family member dubbed SARS-COV 2 and the disease termed as COVID-19 by the World Health Organization (WHO).1

Despite increasing number of mutant strains being reported world-wide[2], CDC-2019 nCOVreal time RT-PCR from nasopharyngeal/oropharyngeal swab specimen remains the gold standard for definitive diagnosis of COVID-19.3 Apart from the rapid antigen test (RAT), there are no cost-effective, fast and easily deployable screening tests available currently at mass scale. Rapid antigen test, besides being labor intensive requiring trained personnel in personal protective equipment for sample collection and permitted in designated laboratories in India, also suffers from low sensitivity. The gigantic second wave of COVID-19 in India, which made significant inroads into the hinterland of our country, had made the wait for these diagnostic tests increasingly longer thereby undermining our effort to 'test, track and treat'.

Complete blood count (CBC) can be performed even at the most basic community health care centers. Neutrophilia, lymphopenia and even eosinopenia is well documented in COVID-19 patients.4, 5In a study involving 1099 COVID-19 patients by Guan *et al*, thrombocytopenia was present in almost one-third (36.2%) of their patients.6These deranged CBC parameters and rising neutrophil to lymphocyte ratio (NLR) are clinically used in predicting the disease severity, alongside C-reactive protein (CRP), serum ferritin, procalcitonin, Interleukin-6 (IL-6) and D-dimer.4

The morphological changes in the leucocytes in COVID-19 patients are documented in few studies, mostly in patients who were hospitalized, and none in patients with mild symptoms or asymptomatic contacts.7-13Themorphological abnormalities in white blood cell (WBC) are neither widely recognized nor yet incorporated in management guidelines.

We endeavored to study the morphological changes in neutrophils, lymphocytes and monocytes in confirmed COVID-19 cases with mild to moderate symptoms as well as asymptomatic contacts presenting at an outpatient clinic.

2. Materials and Methods

We conducted this retrospective study at a laboratory providing diagnostic services to patients from semi-urban and rural areas visiting an outpatient clinic at a tier-3 cityin northern India during the first two weeks of May2021. The study included 36 patients, including three families. All, except six asymptomatic contacts, presented with variable constellation of symptoms of upper respiratory tract infection (URTI) like fever, cough, sore throat, and myalgia. Ten patients, additionally, complained of dyspnea. Eleven patients had gastro-intestinal symptoms like abdominal cramps and diarrhea at the onset. Anosmia and ageusia were other frequent complaints in more than two-third of the patients. COVID-19 diagnosis was confirmed by RAT and RT-PCR in 17 and 15 patients respectively performed at government district civil hospital. In four patients, the RT-PCR was negative but computerized tomogram (CT) of chest showed findings of atypical pneumonia typical for COVID-19 (CO-RADS 5). The symptomatic patients presented between 3rd and 8th day of onset of symptoms.

Their clinical details including symptoms, temperature, pulse, respiratory rate and oxygen saturation on room air were noted. Peripheral venous blood samples were collected at presentation in K2 EDTA vials in all 36 patients for CBC and PBF. Additionally blood was also sampled in plain tubes (with clot activators) for CRP in 26 patients. In seven patients with mild disease, CBC and PBF were repeated during OPD visit after 2 weeks of home quarantine.

Blood samples for CBC were run on ABX Micros-ES60 three-part hematology analyzer. The important CBC parameters were noted including hemoglobin, total leucocytes count (TLC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), neutrophil to lymphocyte ratio (NLR) and platelet count. Peripheral blood films were prepared within maximum 1 hour of sample collection and stained with leishman stain. These PBFs were scrutinized by a pathologist for morphological changes in the leucocytes. CRP quantitative estimation was performed using Alere Afinion equipment which works on borate affinity principle (reference range is < 5 IU/L).

3. Results

All our cases were adults with age ranging from 16 years to 71 years, including 23 males and 13 females. Clinically, 20 patients had mild and 10 had moderate diseases per the revised COVID-19 management guidelines published by the Ministry of Health and Family Welfare (MoHFW) of government of India (www.https: //www.mohfw. gov. in). Six patients, belonging to three familial clusters, were asymptomatic at presentation but tested positive for SARS-COV-2.

The TLC was within normal reference range in all but one patient. Absolute neutrophilia (defined as ANC more than $7x10^9$/L) was present in 9 (25%) cases, including 3 patients with moderate, 4 with mild COVID-19 disease and 2 asymptomatic contacts. Lymphopenia (defined as ALC less than $1x10^9$/L) was observedin 9 (25%) patients that included 5 with mild and 4 with clinically moderate COVID-19 disease. Neutrophil to lymphocyte ratio (NLR) exceeding 3.5% was calculated in 16 (44.4%) cases. We did not observe monocytosis in any of our patients. Three females and two males had mild anemia, defined by WHO cut off of hemoglobin level below 12 g/dL and 13 g/dL for females and males respectively. None of our patients had platelet count below $100x10^9$/L. Out of 26 patients in whom CRP was estimated, it was raised in 17 (65.4%) of cases, including 3 patients with moderate disease whose CRP value exceeded 100 IU/L. The quantitative abnormalities in CBC parameters and CRP level are summarized in table 1. [Table 1]

Table 1: CBC parameters and CRP in COVID-19 patients

Case No.	Age/ Sex	Severity	Diagnosis	Hb (g/dL)	TLC ($x10^9$/L)	Platelet ($x10^9$/L)	ANC (per µL)	ALC (per µL)	AMC (per µL)	NLR	CRP (IU/L)
1	48/M	Mild	PCR+	14.4	6.2	153	4604	1426	120	3.22	<5
2	38/F	Mild	PCR+	12.7	3.7	160	2674	900	55	2.97	34
3	47/M	Mild	PCR+	14.3	5.1	166	3652	1040	102	1.3	42
4	16/M	Cont-As	RAT+	14.5	9.5	262	7125	2090	285	3.4	<5
5	22/M	Cont-As	PCR+	13.1	7.2	294	6555	2660	285	2.46	<5
6	42/F	Cont-As	PCR+	12.1	6.6	188	5082	1254	264	4.05	<5
7	62/M	Mild	RAT+	14.9	7.4	302	5846	888	400	6.58	53
8	60/M	Moderate	RAT+	13.2	6	226	4320	1560	120	2.76	83
9	50/M	Moderate	CT chest	16.6	5.5	194	4455	825	110	5.4	NT
10	48/F	Mild	PCR+	13.8	5.7	305	4275	1368	57	3.12	<5
11	71/M	Moderate	PCR+	15	10.1	193	8585	1313	202	6.53	160
12	68/F	Moderate	RAT+	12.5	4.5	119	4230	225	45	18.8	140
13	65/M	Mild	PCR+	13.3	9.4	211	8554	846	50	10.1	84
14	70/F	Mild	RAT+	13.1	3.8	158	2479	1184	38	2.09	8
15	64/M	Mild	RAT+	13.3	10.1	183	8080	1818	101	4.44	46
16	60/F	Mild	PCR+	13.4	4.2	106	3444	630	84	5.46	8
17	54/M	Mild	PCR+	13.6	10.8	325	9180	1512	108	6.07	<5
18	51/M	Mild	PCR+	15	4.1	206	2706	1230	164	2.2	<5
19	47/M	Mild	RAT+	15	7.5	218	5025	1650	750	3.04	28
20	50/M	Moderate	PCR+	16	5.7	187	3990	1596	114	2.5	20
21	48/F	Mild	RAT+	10.4	4.2	204	2772	1092	294	2.53	NT
22	16/M	Moderate	RAT+	11	5.3	260	3604	1431	265	2.51	125

23	36/M	Mild	RAT+	13.3	6.6	187	4488	1980	66	2.26	NT
24	30/M	Moderate	CT chest	12	3.6	158	2808	792	50	3.54	20
25	20/M	Mild	PCR+	14	11	446	8910	1540	110	5.78	NT
26	51/M	Mild	RAT+	16.2	7.4	199	4736	2368	148	2	<5
27	48/F	Mild	PCR+	11.1	5.7	162	4500	969	50	4.64	20
28	26/M	Cont-As	RAT+	16.9	8.3	295	6308	1743	100	3.61	NT
29	24/F	Cont-As	RAT+	13.3	10.1	232	7575	2222	303	3.4	NT
30	22/F	Moderate	CT chest	12.7	11.3	247	9266	1582	452	5.85	75
31	19/M	Mild	RAT+	16.3	7.6	161	4636	2888	76	1.6	<5
32	65/F	Moderate	CT chest	13.4	7.1	169	4828	1846	355	2.6	25
33	55/M	Mild	RAT+	14.9	4.8	158	3072	1680	48	1.8	NT
34	45/F	Cont-As	RAT+	11.7	7.7	131	6059	1168	300	5.2	NT
35	50/F	Mild	PCR+	13.3	5.8	154	3604	2146	50	1.7	NT
36	42/M	Moderate	RAT+	15.3	19.4	262	18528	579	200	32	NT

Abbreviations: RAT: Rapid antigen test; Hb: hemoglobin; TLC: Total leucocyte count; ANC: Absolute neutrophil count; ALC: Absolute lymphocyte count; AMC: Absolute monocyte count; NLR: Neutrophil lymphocyte ratio; CRP: C-Reactive Protein

Irrespective of absolute neutrophil count, a plethora of morphological changes were observed in the neutrophilsin all but two cases. Two prominent observations were presence of spike like projections on the surface of nuclear membrane (80%) and abnormal nuclear shape and segmentation (75%). Both hypersegmentedandhypolobated nuclei were noted. Many neutrophils had abnormal nuclear shapes including ring nuclei and embryo shaped nuclei. In nearly half of ourcases (47%), significant percentage of neutrophils exhibitedhypogranular cytoplasm and Howell-Jolly body-like inclusions were present in the cytoplasm of neutrophil in approximately one-third patients (33%). [Figure 1] We did not observe toxic granulations or significant shift to left in neutrophilic series.

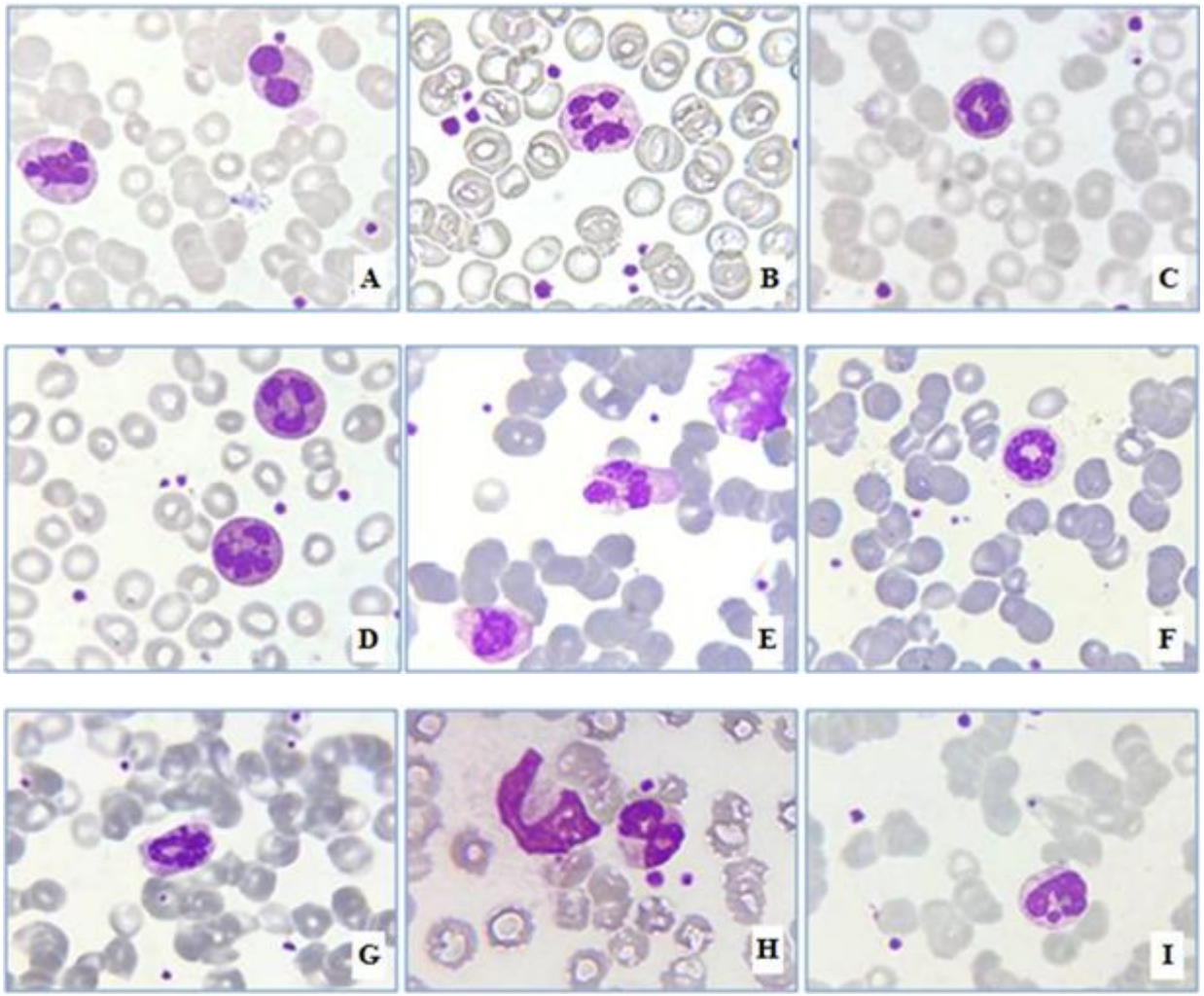

Figure 1: Morphological abnormalities in neutrophils (Leishman stain; 1000x) A: Hypolobation of nucleus, nuclear spikes; B: Hypersegmented neutrophil with nuclear spikes; C: Ring shaped nuclei with spikes; D: Nuclear spikes; E: Abnormal nuclear shape in neutrophil (& monocyte); F: Ring shaped nuclei &hypogranular cytoplasm; G: Pi shaped nuclei with spikes; H: Abnormal double ring nuclear shape; I: Howell-Jolly body like inclusion in neutrophil.

In 14 (38.8%) patients with normal ALC and 7 (19.4%) with lymphopenia, a conspicuous morphological abnormality noted was presence of reactive/plasmacytoid lymphocytes with moderate amount of deep blue cytoplasm and slightly eccentric nuclei. In one-third of these patients, a peculiar observation was irregular cytoplasmic border with feathery appearance of the cytoplasm oflymphocytes. Large granular lymphocytes were not a significant finding in our cases. Despite normal AMC, monocytes exhibited abnormal coalescent cytoplasmic vacuoles in 17 (47.2%) patients. [Figure 2]

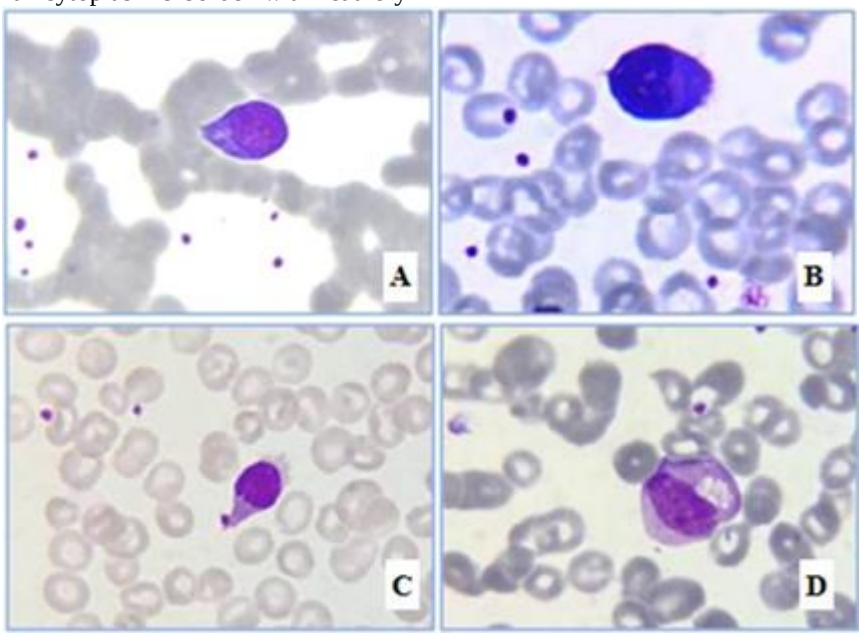

Figure 2: Morphological abnormalities in neutrophils (Leishman stain; 1000x) A & B: Reactive lymphocytes with eccentric nuclei and deep blue cytoplasm (note feathery projections of cytoplasmic border in B); C: Feathery projections of cytoplasmic border of lymphocyte; D: Abnormal coalescent vacuoles in monocyte cytoplasm.

The morphological abnormalities in neutrophils, lymphocytes and monocytes are summarized in table 2. [Table 2]

Table 2: WBC morphology in COVID-19 patients

Case No.	Age/ sex	Severity	Neutrophils				Lymphocytes		Monocytes
			Nuclear spikes	Abnormal nuclear shapes & segments	Howell-Jolly body like inclusions	Abnormal cytoplasm granules	Reactive/ Plasmacytoid	Irregular cell border	Abnormal cytoplasm vacuoles
1	48/M	Mild	+	+	-	-	-	-	+
2	38/F	Mild	+	+	-	-	-	-	-
3	47/M	Mild	+	+	+	+	+	-	+
4	16/M	Contact-As	+	-	-	-	-	-	+
5	22/M	Contact-As	+	-	-	-	-	-	+
6	42/F	Contact-As	+	+	-	-	+	+	+
7	62/M	Mild	+	+	-	+	+	-	+
8	60/M	Moderate	+	+	-	+	-	-	+
9	50/M	Moderate	-	+	-	-	+	+	-
10	48/F	Mild	-	+	-	-	-	-	-
11	71/M	Moderate	+	+	+	+	-	-	+
12	68/F	Moderate	+	+	-	+	-	-	-
13	65/M	Mild	+	+	+	+	+	+	-
14	70/F	Mild	-	-	-	-	+	-	+
15	64/M	Mild	+	+	+	+	+	-	-
16	60/F	Mild	+	+	-	-	+	+	-
17	54/M	Mild	+	+	-	-	+	-	-
18	51/M	Mild	+	-	-	-	-	-	-
19	47/M	Mild	+	+	+	+	-	-	+
20	50/M	Moderate	+	+	-	-	+	-	-
21	48/F	Mild	-	+	-	-	+	-	+
22	16/M	Moderate	+	+	+	+	+	+	-
23	36/M	Mild	+	-	-	-	-	-	-
24	30/M	Moderate	+	+	-	+	+	+	-
25	20/M	Mild	+	+	-	-	-	-	+
26	51/M	Mild	-	-	+	-	+	-	-
27	48/F	Mild	+	+	+	+	+	+	+

28	26/M	Contact-As	+	-	+	-	-	-	-
29	24/F	Contact-As	+	+	-	-	-	-	-
30	22/F	Moderate	+	+	+	+	+	-	+
31	19/M	Mild	-	-	-	+	+	-	-
32	65/F	Moderate	+	+	+	+	+	-	+
33	55/M	Mild	+	+	-	+	+	-	-
34	45/F	Contact-As	-	-	-	-	+	-	+
35	50/F	Mild	+	+	-	+	+	-	-
36	42/M	Moderate	+	+	+	+	-	-	+

In seven mild COVID-19 patients who had CBC and PBF repeated after 2 weeks, no cytopenia was present and all the morphological abnormalities in neutrophils had disappeared but activated lymphocytes persisted in three patients.

4. Discussion

Since the pandemic hit in 2019, numerous original publications as well as review articles have chronicled the numerical abnormalities in hematological parameters associated with SARS-COV-2 infection. Early investigators in China quickly observed and reported lymphopenia in COVID-19 patients not only as a very common hematological finding but also heralding progression to severe disease.[4, 6, 14] The subset of lymphocyte that is most afflicted is the cytotoxic CD8+T cells and natural killer (NK) cells attributable to functional exhaustion of hyper-activated lymphocytes.[4, 15]The jury is still out on absolute monocyte count in COVID-19. Yun *et al.* observed monocytosis in COVID-19 patients compared to influenza patients.[16]Contrastingly Sun *et al.* reported monocytopenia in severe COVID-19 patients in ICU.[17]Zhang *et al.* did not observe any statistical difference in monocyte count between COVID-19 patients and healthy individuals.[18]Significant neutrophilia is frequently observed in COVID-19 patients, with rising count in critically ill patients requiring ICU admission.[5, 9]Terpos *et al.*, in their review article, summarized that rising neutrophilic leucocytosis predicts increased risk of acute respiratory distress syndrome and death.4Neutrophil to lymphocyte (NLR) ratio is now widely utilized as a vital prognostic parameter in COVID-19 patients.[4, 19]Alongside lymphopenia and neutrophilia, many studies have also highlighted worsening eosinopenia in severe and critically ill COVID-19 patients and conversely a rising esoinophil count during recovery.[5, 18, 20]

The numerical abnormalities in WBCs are widely recognized and even incorporated in clinical management guidelines particularly in predicting risk of severe disease and death. However, literature on morphological abnormalities in leucocytes and their clinical significance is still sparse and hitherto described only in patients who were hospitalized.

Despite normal total leucocyte counts in all but one of our patients, PBF examination revealedconstellation of morphological abnormalities in the WBCs even in those who were asymptomatic. Neutrophil nuclear spikes, abnormal lobation and shapes werevery common observations. Howell-Jolly body-like inclusions in neutrophil cytoplasm was another significant finding in one-third of our patients. Kaur and her colleagues, in their analysis of PBF findings on 20 hospitalized COVID-19 patients also frequently observed pseudo-Pelger-Huet abnormality, dysmorphic nuclei and abnormal nuclear projections in neutrophils.[10]Toxic granulations and shift to left in neutrophilic series were also prominent findings by Kaur *et al* as well as Nazarullah*et al,* which we did not observe in our patients.[10, 11]Many investigators also reported presence of smudged neutrophils in PBF of COVID-19 patients.[10, 13]A study by Nath *et al.* conducted during the first wave of COVID-19 from Northern India also observed similar dyspoietic features in neutrophils.[12]However, abnormal nuclear shapes in neutrophils were neither a prominent finding norwas it specific to COVID-19 patients in the study by Pozdnyakova*et al*.9But, like us, they also observed Howell-Jolly body-like inclusions in neutrophils in 10% cases. The authors concluded that while neutrophilia and lymphopenia were more prevalent in severe disease, the PBF of patients with mild disease exhibited more morphological abnormalities in agranulocytes.9Shahri*et al.* in their review article summarized thatthese morphological abnormalities usually normalized after treatment as was observed in seven of our patients with mild symptoms whose repeat CBC and PBF after two weeks showed neutrophils with normal morphology.5

Significant percentage of circulating lymphocytes appeared reactive/ plasmacytoid in 58.3% of our patients. Some of these lymphocytes had irregular cell border with feathery appearance. In the study by Merino *et al.*, 1% to 15% of circulating lymphocytes were reactive exhibiting plasmacytoid morphology with eccentric nuclei, coarse clumped chromatin, often a prominent nucleolus and moderate amount of deep blue cytoplasm.8 Nath *et al.* also made similar observation in COVID-19 patients during the first wave in India, and proposed to call them covicytes.[12]Atypical and plasmacytoid lymphocytes were also observed by Pozdnyakova *et al.* along with cytoplasmic vacuolations and large granular lymphocytes.9 Abnormal shapes and coalescent vacuoles in monocytes were other significant finding in PBF of our patients.[9, 10]Zhang *et al.* documented that despite no abnormality in absolute monocyte count, the monocytes in COVID-19 patients are functionally abnormal with increased release of pro-inflammatory cytokines, reflected by elevated serum levels of inflammatory marker IL-6 during cytokine storm.[18]

A national positivity rate that soared above 20% during the peak of second wave COVID-19 pandemic put humungous pressure even on an increasingly ramped up laboratory and hospital services. This underscores the necessity of an inexpensive and ubiquitously available screening test for guiding quick clinical diagnosis in outpatient clinics. Peripheral blood film screening for features of dyspoiesis in leucocytes which are overwhelmingly present in COVID-19 patients even in the absence of deranged WBC counts, can

become instrumental in quickly gauging the effects of SARS-COV-2 infection.

Viral infections are known to induce morphological changes in WBCs, particularly in lymphocytes. We in India are accustomed to recognize reactive or plasmacytoid lymphocytes in PBF, particularly during Dengue outbreaks. But COVID-19 induces a wide range of quantitative and qualitative changes in both granulocytes and agranulocytes. The number of patients included in our study is small and comparison with non-COVID febrile URTI patients as well as healthy group could not be performed during the peak of pandemic. Follow up CBC and PBF was also possible in only few patients. But in the face of myriads of leucocyte morphological abnormalities observed in the PBF of even asymptomatic contacts, a study on a larger number of cases and more importantly comparison with appropriate control groups is warranted to further elucidate the significance of WBC morphology and its promising role in guiding quick clinical diagnosis.

Conflict of interest: None

References

[1] Coronavirus disease (COVID-19). Situation Report – 124. Geneva: World Health Organization; 2020. https: //www.who. int/docs/default-source/coronaviruse/situation-reports/20200523-covid-19-sitrep-124. pdf?sfvrsn=9626d639_2. Accessed May 25, 2021.

[2] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, *et al*. A novel coronavirus from patients with pneumonia in China, 2019. N. Eng. J. Med.2020; 382 (8): 727–733.

[3] Koyama T, Platt D, Parida L. Variant analysis of SARS-COV-2 genomes. Bull World Health Organ.2020; 98 (7): 495-504.

[4] Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politau M, *et al*. Hematological findings and complications of COVID-19. Am J Hematol.2020; 95 (7): 834-847.

[5] Shahri MK, Niazkar HR, Rad F. COVID-19 and hematology findings based on the current evidences: A puzzle with many missing pieces. Int J Lab Hematol.2021; 43: 160–168.

[6] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, *et al*. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med.2020; 382 (18): 1708-1720.

[7] Singh A, Sood N, Narang V, Goyal A. Morphology of COVI-19 affected cells in peripheral blood film. BMJ Case Rep.2020; 13e236117.

[8] Merino A, Vlagea A, Molina A, Egri N, Laguna J, Barrera K, *et al*. Atypical lymphoid cells circulating in blood in COVID-19 infection: morphology, immunophenotype and prognosis value. J Clin Pathol.2020 Dec: jclinpath-2020-207087.

[9] Pozdnyakova O, Connell NT, Battinelli EM, Connors JM, Fell G, Kim AS. Clinical Significance of CBC and WBC Morphology in the Diagnosis and Clinical Course of COVID-19 Infection. Am J Clin Pathol; 2020; XX: 1–11.

[10] Kaur G, Sandeep FNU, Olayinka O, Gupta G. Moprhological changes in circulating blood cells of COVID-19 patients. Cureus.2021; 13 (2): e13416.

[11] Nazarullah A, Liang C, Villarreal A, Higgins RA, Mais DD. Peripheral blood examination findings in SARS-CoV-2 infection. Am J Clin Pathol.2020; 154 (3): 319-329.

[12] Nath D, Madan U, Singh S, Tiwari N, Madan J, Agrawal R. CBC parameters and morphological alterations in peripheral blood cells in COVID-19 patients: Their significance and correlation with clinical course. Int J Health Clin Res.2020; 3 (10): 95-108.

[13] Sadigh S, Massoth LR, Christensen BB, Stefely JA, Keefe J, Sohani AR. Peripheral blood morphologic findings in patients with COVID-19. Int J Lab Hematol.2020; 42 (6): e248-e251.

[14] Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Deng Y, *et al*. Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A systemic review and meta-analysis. Int J Infect Dis.2020; 96: 131-135.

[15] Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, *et al*. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol.2020; 17 (5): 533–535.

[16] Yun H, Sun Z, Wu J, Tang A, Hu M, Xiang Z. Laboratory data analysis of novel coronavirus (COVID-19) screening in 2510 patients. Clin Chim Acta.2020; 507: 94-97.

[17] Sun S, Cai X, Wang H, He G, Lin Y, Lu B, *et al*. Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. Clin Chim Acta.2020; 507: 174-180.

[18] Zhang J-J, Dong X, Cao Y-Y, Yuan Y-D, Yang Y-B, Yan Y-Q, *et al*. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy.2020; 75 (7): 1730-1741.

[19] Kong J, Wang T, Di Z, Shi B, Yu X, Huang C*et al*. Analysis of hematological indexes of COVID-19 patients from fever clinics in Suzhou, China. Int J Lab Hematol.2020; 42 (5): e204-e206.

[20] Yan B, Yang J, Xie Y, Tang X. Relationship between blood eosinophil levels and COVID-19 mortality. World Allergy OrganJ.2021; 14 (3): 100521.