A Review of Morphologic Findings in Peripheral Blood Smears of COVID-19 Patients

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ABSTRACT

Introduction: Peripheral smear examination is a simple and cost-effective test that is routinely performed while monitoring patients diagnosed with COVID-19. We sought to summarize the peripheral blood morphologic findings in patients with COVID-19 infection.

Methods: A systematic review was conducted using a standardized keyword search on Medline database (PubMed), med RXIV, Google Scholar, EMBASE, and SCOPUS for studies discussing peripheral blood smear or morphologic blood findings in patients diagnosed with COVID-19.

Results: A total of 28 studies were included in the review. Normocytic normochromic anemia was the most frequently encountered red blood cell finding. Neutrophilia was seen in most of the studies. A variety of morphological changes were observed in neutrophils, including pyknotic nuclei, variable shapes, toxic granules, and cytoplasmic vacuolization. Hyposegmented neutrophils, pseudo-Pegler Huet forms, and hypogranular forms were common findings reported by many studies. Lymphopenia was reported by most studies. Lymphocytes showed numerous morphological changes, including reactive forms, Downey forms, increased large granular lymphocytes, and plasmacytoid cells. The presence of giant platelets was seen frequently.

Conclusions: The peripheral blood in COVID-19 shows a spectrum of findings, mostly reactive changes in neutrophils, monocytes, lymphocytes, and platelets. Increased neutrophil/lymphocyte ratio and higher neutrophil counts have been associated with poor prognosis, which potentially could help triage patients, but this needs to be confirmed in larger studies.

INTRODUCTION

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), first emerged in Wuhan, China. The virus spread very rapidly across countries and quickly emerged as a global pandemic, drastically affecting health worldwide. Based on the favorability of viral spread, there have been abrupt surges in cases causing so-called "waves." The omicron and delta variants of SARS-CoV-2 emerged by undergoing mutations and have proven to be highly contagious and deadly. Despite the implementation of various prevention measures, such as social distancing, contact tracing, and mandatory vaccination, COVID-19 remains a major health concern causing a high number of fatalities.[1-3]

Several studies have reported the complex pathophysiology of COVID-19, including immune dysregulations and various hematologic manifestations. Viral infections are known to affect hematopoiesis both quantitatively and qualitatively. HIV infections, cytomegalovirus infections, infectious mononucleosis, SARS, and COVID-19 infection have been associated with atypical lymphocytes.[4-6]

The morphologic changes in peripheral blood have not been studied extensively. To our knowledge, no comprehensive review of the literature describing the peripheral blood morphologic findings in patients diagnosed with COVID-19 has been published. This review aims to summarize the literature to date.

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METHODS

Literature Search Strategy

A systemic search of the literature was conducted in the electronic databases following the preferred reporting items for systematic reviews and meta-analysis guidelines. We searched in the Medline database (PubMed), med RXIV, Google scholar, EMBASE, and SCOPUS, with the combined terms "novel coronavirus," "2019 novel coronavirus," "SARS – COV-2," "COVID-19," and "periph-

eral blood smear" or "morphologic peripheral blood findings." Additional studies were identified by studying the references of the original studies and pertinent review articles. Three researchers examined the databank.

Selection and Exclusion Criteria

Searches were limited to publications before January 31, 2022. Papers published in English were included. Original articles, clinical analysis, and research discussing the peripheral blood smear manifestations of COVID-19 were included. Unavailable articles, medical hypotheses, and duplicate articles were excluded. Cases with the clinical diagnosis of disease were included, in addition to cases of COVID-19 confirmed by viral nucleic acid detection, viral gene sequencing, and serum antibody test. Due to the scarcity of studies reporting peripheral blood morphologic findings in COVID-19, case reports were included. The following exclusion criteria were applied: case reports of other coronaviruses, animal studies, and studies that did not describe the peripheral blood morphologic findings in humans.

Data Extraction

Data extraction was performed independently by two authors and discrepancies were resolved by consensus. Full-text articles were retrieved for detailed review. We used standardized forms that included author, year, study design, age, and gender.

RESULTS

Study details including year, article type, title, and number of smears studied, as well as patient demographics (eg, country, age, and sex) are enumerated in Table 1.[7-31] Morphologic findings of red blood cells, neutrophils, lymphocytes, platelets, and additional findings are enumerated in Table 2.[7-31] and have been summarized in Table 3. These findings are further elaborated in this section.

Red Blood Cells

Anemia was the most frequently encountered red blood cell finding, reported by 8 studies. Luke et al,[17] Mitra et al,[18] and Pozdnyakova et al[21] reported cases with nucleated red blood cells. Pezeshki et al reported a relatively higher number of cases with schistocytes,[20] and Schapkaitz et al reported cases showing red cell fragments.[23] Overall, hemolytic changes were not a predominant finding in most of the studies.

White Blood Cells

Neutrophil counts were reported in 16 of the 28 studies. Twelve studies reported neutrophilia, 1 study documented neutropenia, and 3 studies included some patients with neutrophilia and others with neutropenia. A variety of morphological changes were observed in neutrophils, including toxic granulation (7 studies), pyknosis (2 studies), hyposegmentation (7 studies), hypersegmentation (2 studies), Pelget Huer anomaly (7 studies), and other findings (11 studies). Berber et al saw pyknotic neutrophilic nuclei in their patient group,[6] as did Nazarullah et al in rare cases.[19]

Singh et al reported striking morphologic changes in the neutrophils358– ring-shaped, C-shaped, and fetus-like nuclei; heavily clumped nuclear chromatin; aberrant nuclear projections; and elongated nucleoplasm. They lumped these findings together and described them as COVID nuclei.[24] In addition, they found toxic granules and cytoplasmic vacuolization in neutrophils, which also were seen by Kaur et al14 and Pozdnyakova et al.[21] Cantu et al found only toxic granules without any vacuoles and also reported blue-green inclusions in neutrophils in 6 cases.[10]

Luke et al, the only researchers to study the electron microscopic findings of peripheral blood elements, found multiple aberrancies in all hematopoietic lineages as described in the Tables.[17] Hyposegmented neutrophils, pseudo-Pelger Huet forms, and hypogranular forms were common findings reported by many studies.

Lymphocyte counts were reported in 18 of the 28 studies, and lymphopenia was the predominant finding in all 18 studies. The presence of reactive lymphocytes was documented in 19 studies irrespective of lymphocyte counts. Reactive lymphocytes showed various morphological forms, including Downey forms (7 studies) and plasmacytoid cells (10 studies). Kubik et al described the plasmacytoid lymphocytes, immunoblastic cells, and plasma cells as "covidocytes."[25] Morphological forms, such as smudge cells (2 studies) and apoptotic cells (2 studies), also were seen. Luke et al observed other morphological features, including multilobulated nuclei and large cytoplasmatic granulations in lymphocytes.[17] Bahadur et al reported azurophil granules and prominent nucleoli in lymphocytes.[9] Tummiddi et al found cytoplasmic pods, vacuolations, and nuclear blebbing.[26] Seven studies reported increased large granular lymphocytes. Kubik et al found increased granulation in the large lymphocytes.[25] Luke et al studied the electron microscopic findings of the reactive lymphocytes and found features such as nuclear lobulation and invagination, elongation of lymphocytes, enlarged lymphocytes with basophilic cytoplasm, and undergoing apoptosis with signs of karyolysis.[17]

Monocyte count changes were reported in 5 studies, with two documenting monocytosis and three reporting monocytopenia. Four studies reported an increase in monocyte size, and 12 studies found cytoplasmic vacuolation of the monocytes.

Morphologic findings in eosinophils were reported by only a few studies. One study reported a decrease in eosinophil count with COVID-19 infection,[6] while cytoplasmic vacuoles were seen in eosinophils in studies by Ahnach et al[7] and Pozdnyakova et al.[21]

Platelets

A common morphologic finding in platelets was the presence of giant forms. Platelet counts were documented in 6 of the 28 studies. Thrombocytopenia was reported in 3 studies, thrombocytosis was reported in 1 study, and 2 studies documented both thrombocytosis and thrombocytopenia. Morphological changes documented in platelets included giant forms (11 studies), large forms (1 study), platelet clumps or aggregates (3 studies), platelet

Table 1. Demographic and Clinical Characteristics of Patients in the Included Studies

Author (month, year)	Article Type	Country	Age	Sex	No. of COVID Smears Studied
Ahnach et al (12/20)[7]	Letter	Morocco	N/A	N/A	15
Akçabelen et al (03/21)[8]	Images	Turkey	16	F	1
Bahadur et al (10/21)[9]	Original	India	42.16 ± 15.55 y	M 35, F 15	50
Berber et al (01/21)[6]	Original	Turkey	44 (range 18–88 y)	M 25, F 25	50
Cantu et al (06/20)[10]	Letter	New York, USA	N/A	N/A	6
Chong et al (04/20)[11]	Images	Singapore	N/A	N/A	32
El Jamal et al (06/20)[5]	Correspondence	New York, USA	N/A	N/A	33
Gerard et al (06/20)[4]	Images	France	74	F	1
Gabr et al (01/22)[12]	Original	Egypt	60.68 ± 13.04 (24–89 y)	M 65 (57.5%), F 48 (42.5%)	113
Harris et al (04/21)[13]	Original	Boston, MA, USA	32 to > 89; median, 63 y	M 12, F 8	20
Kaur (02/21)[14]	Original	Danbury, CT, USA	65.1	M 13, F 7	20
Lee et al (08/20)[15]	Images	Singapore	60	M 1	1
Liu et al (11/20)[16]	Letter	China	31–83	F 12	23
Luke et al (06/20)[17]	Original	Germany	58 (21–77 y)	M 30 (67%), F 15 (33%)	45
Mitra et al (04/20)[18]	Images	California, USA	46 y	F 1	1
Nazarullah et al (08/20)[19]	Original	Texas, USA	55 (25–100 y)	M 7, F 5	12
Pezeshki et al (07/21)[20]	Original	Isfahan, Iran	10–90 y	M 54 (60.7%), F 35 (39.3%)	89
Pozdnyakova et al (02/21)[21]	Original	Boston, USA	58.66 (non-ICU group) 64.12 (ICU group)	M/F ratio: 0.56 (non-ICU group) 1.55 (ICU group)	90
Sadigh et al (07/2020)[22]	Letter	Massachusetts, USA	52.6 (28–80 y) COVID+ group	M 17, F 10	78
Schapkaitz et al (12/20)[23]	Letter	South Africa	Median, 49 y	M/F ratio: 1.2:1	59
Singh et al (05/20)[24]	Images	India	55 y	F	1
Kubik et al (01/22)[25]	Original	Canada	Mean, 58 years (20–98 y)	M 30, F 24 (discovery set) M 38, F 21 (validation set)	113 (total)
Tummidi et al (04/21)[26]	Case report	India	58 y	F	1
Weinberg et al (06/20)[27]	Correspondence	Illinois, USA	26–90 y	M 8, F 7	15
Yarali et al (05/20)[28]	Letter	Turkey	8.11 ± 5.71 y (4 m–17 y)	N/A	30 (COVID+ cases)
Yuki et al (09/21)[29]	Original	Japan	61 (46–67 y)	M 30 (75.0%) F 10 (25.0%)	40 (COVID+ cases)
Zhang et al (09/20)[30]	Original	China	N/A	N/A	34 patients
Zini et al (04/20)[31]	Images	Italy	N/A	N/A	40

Abbreviations: F, female; M, male; y, years; ICU, intensive care unit; N/A, not available.

Table 2. Morphologic Findings of Red Blood Cells (RBC), Neutrophils, Lymphocytes, Platelets, and Additional Findings

Author	RBC	Neutrophils	Lymphocytes	Platelets	Other
Ahnach et al[7]	N/A	Hyposegmented, hypogranular	Lymphopenia (46%), reactive forms	Giant forms	Monocytosis (9.5%), large moncytes; eosinophils: vacuoles
Akçabelen et al[8]	N/A	Hypersegmented, pseudo Pelger-Huet forms	Reactive forms	Giant forms	Monocytes: vacuoles
Bahadur et al[9]	Normocytic normochromic (76%)	Toxic changes, hyposegmented forms, nuclear projections 9 (18%), ring nuclei 7 (14%)	Azurophil granules 6 (12%), prominent nucleoli 5 (10%)	Giant platelets 28 (56%)	Monocytes: vacuoles, monocytes clumped nuclear chromatin 6 (12%), cytoplasmic granules 4(8%)
Berber et al[6]	N/A	Neutropenia, pyknotic, hypogranular, pseudo Pelger-Huet: 10 (median), dysplastic neutrophils, pyknosis, karyolysis, karyorrhexis	Decreased counts, reactive forms, Downey forms	N/A	Eosinophils: Decreased counts; monocytes: vacuoles
Cantu et al[10]	N/A	Toxic changes, green blue inclusions	N/A	N/A	N/A
Chong et al[11]	N/A	N/A	Reactive forms, plasmacytoid forms	N/A	N/A
El Jamal[5] et al[5]	N/A	N/A	Reactive forms, Downey forms, plasmacytoid forms	N/A	N/A
Gerar et al[4]	N/A	Increased counts	Downey forms	N/A	N/A
Hala Gabr et al[11]	N/A	Toxic forms, hypogranular, pseudo Pelger-Huet, pyknotic forms w fragmented (karyorrhectic) nuclei w intense basophilic chromatin and broken forms	Reactive, vacuolated forms; plasmacytoidforms	N/A	Monocytes: vacuoles, apoptotic eosinophils. Dysplastic cells of myeloid origin. Mott cells.
Harris et al[13]	Anemia (6 cases)	Increased counts	Decreased counts	Decreased counts,	Plasma cells giant forms

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Table 2 continued. Morphologic Findings of Red Blood Cells (RBC), Neutrophils, Lymphocytes, Platelets, and Additional Findings

Author	RBC	Neutrophils	Lymphocytes	Platelets	Other
Kaur et al[14]	Anemia (17 cases), coarse basophilic stippling, nucleated RBCs	Toxic changes, hyposegmented, pseudo Pelger-Huet forms, hypersegmented forms vacuolization, abnormal nuclear shapes and aberrant nuclear projections; smudged neutrophils	Reactive, Downey, large granular, plasmacytoid forms	Platelet clumps	Smudge cells left shift
Lee et al[15]	N/A	N/A	Decreased counts; reactive, Downey, large granular, plasmacytoid forms	N/A	Plasma cells
Liu et al[16]	N/A	N/A	Reactive, plasmacytoid forms	N/A	N/A
Luke et al[17]	Nucleated RBCs, basophilic stippling, stomatocytes	Hyposegmented, hypergranular (35), pseudo Pelger-Huet (21), LM: hypergranular (35), aberrant nuclear segmentation; EM: early stages of apoptosis, hypercondensed chromatin, nuclear shrinking	36 (80%) abberant forms; 5 (9%) reactive forms. EM: nuclear lobulation and invagination; elongation of lymphocites, enlarged lymphocyte w basophilic cytoplasm, undergoing apoptosis with signs of karyolysis), plasmacytoid forms	Giant forms, platelet clumps	Monocytes w aberrant nuclei (clumped chromatin) and basophilic cytoplasm, plasma cells, left shift
Mitra et al[18]	Normocytic anemia nucleated	Increased count	Decreased count	Large forms	N/A
Nazarullah et al[19]	N/A	Toxic changes (4/12), pseudo Pelger-Huet (12), rare pyknotic forms, apoptotic changes	Decreased count Downey forms (types 1,2,3), large granular and plasmacytoid forms	N/A	Left shift
Pezeshki et al[20]	Schistocytes (24, 27%)	N/A	Reactive and large granular forms	Giant forms	Leucoerythroblastic reaction, left shift, smudge cells
Pozdnyakova et al[21]	Nucleated RBCs	Toxic changes, hypogranular forms, cytoplasmic vacuolization, Howell-Jolly body-like inclusions, and Döhle bodies	Reactive, large granular, plasmacytoid	N/A	Monocytes: large coalescing cytoplasmic vacuoles; eosinophils: cytoplasmic vacuoles
Sadigh et al[22]	Anemia, 13 dysmorphic, 14 normal	Smudged neutrophils	Decreased lymphocyte count, reactive and plasmacytoid forms	Giant forms	Plasma cells
Schapkaitz et al[23]	RBC fragments >1%	Increased counts, hyposegmented forms, hypogranular forms, pseudo Pelger-Huet forms (60/102)	Lymphopenia (49/102), severe lymphocytopenia (19/102), reactive large granular, plasmacytoid forms	Increased counts, giant forms	Monocytes: decreased counts, vacuoles. Plasma cells. Leuko erythroblastic reaction, left shift.
Singh et al[24]	N/A[a]	Increased counts, toxic changes, heavily clumped chromatin, nuclear abnormalities	Decreased counts, large granular forms, apoptotic lymphocytes	Few giant forms	Monocytes: decreased counts, vacuoles
Kubik et al[25]	N/A	Abnormal absolute neutrophil counts (either 2000/IL or 9000/IL)	Absolute lymphopenia, absolute large granular lymphocyte counts >300/IL, enriched in cases w/out lymphopenia; covidocytes (plasmacytoid w/out lympho cytes, immunoblastic cells, plasma cells)	Platelet aggregates	Monocytes: increased count; smudge cells
Tummidi et al[26]	Normochromic normocytic	Hyposegmented, hypogranular, ring shape, club shape, U shape, fetal-like, satellitism	Increased granulation in large lymphocytes, cytoplasmic pods, vacuolations, nuclear blebbing	Platelet satellitism, giant forms	Monocytes: vacuoles, abundant cytoplasm with granulations, nuclear blebbing, irregular cytplasmic membranes; smudge cells
Weinberg et al[27]	Normocytic anemia mild anisopoikilocytosis, no hemolysis	Increased counts predominated	Decreased counts, reactive and Downey 2 forms, plasmacytoid forms	N/A	N/A
Yarali et al[28]	Anemia, 1/70	Increased and decreased counts, hypergranulation/lobulation abnormalities in neutrophils (n = 11; 36.7%)	Decreased counts, reactive forms	Decreased counts, giant forms	Monocytes: vacuoles
Yuki et al[28] `	Polychromatic RBCs, hypochromic RBCs, schistocytes	Increased absolute neutrophil counts; toxic changes, Dohle body, vacuoles, giant forms; neutrophil dysplasia: increased acquired Pelger-Huët anomaly and monolobated neutrophils, degranulation/hypogranulation, and chromatin abnormality	Lower absolute lymphocyte count; vacuoles, reactive forms, granular lymphocyte	Giant forms	Increased neutrophil-lymphocyte ratio
Zhang et al[30]	N/A	N/A	N/A	N/A	Monocytes: increased counts, large forms, with vacuoles
Zini et al[31]	N/A	Increased counts, toxic changes, pseudo Pelger-Huet forms, hypogranular forms, nuclear and cytoplasmic granulation. Preapoptotic and apoptotic cells	Decreased counts, reactive large granular,plasmacytoid forms	Large, hyperchromatic, vacuolated forms	Apoptotic forms, left shift

Abbreviation: N/A, not available.
[a]The study did not report this parameter.

satellitism (1 study), giant forms with clumping (1 study), and large, hyperchromatic, vacuolated forms (1 study). Various other changes also were reported, including leucoerythroblastic reaction (2 studies), left-shifted maturation (8 studies) and apoptotic forms (1 study), and smudge cells (4 studies).

DISCUSSION

Neutrophilic leukocytosis is frequently observed in COVID-19 cases, but the cause remains uncertain. Bacterial or fungal coinfection may play a role secondary to lowered immune function and has been described in a few patients from Wuhan and in additional studies.[32-34] However, Harris et al and others have reported neutrophilia in the absence of superimposed infections, suggesting patients with COVID-19 and no known coinfections can nevertheless develop a pronounced neutrophilic leukocytosis.[13]

Several studies also have found associations between higher neutrophil counts with worse outcomes. Singh et al reported characteristic nuclear findings in neutrophils, along with morphological changes in lymphocytes and monocytes. The neutrophils showed peculiar morphological changes that have not been reported frequently. However, these features were restricted to only 1 case.[24] Cantu et al found that neutrophilic green inclusions were identified more than 20 days after COVID-19 testing and that these patients had acutely elevated transaminases, lactate dehydrogenase, and lactic acid.[10] Prior studies have postulated that these inclusions may be derived from the lipofuscin released from necrotic hepatocytes.[35-37] Due to poor prognosis and death shortly after the identification of these inclusions, Cantu et al red-flagged the presence of these inclusions as a higher risk factor for short-term mortality in COVID cases.[10]

Luke et al studied both the light and electron microscopic findings in 45 cases. They studied their cohort extensively after negative SARS-CoV-2 testing and found that as the infection subsided and systemic inflammation decreased, granulopoiesis showed only mild morphologic changes, such as improvement in the left shift.[17] Thus, to analyze the recovery of the hematopoietic system, follow-up of these patients systematically on a long-term basis will prove beneficial. This would also facilitate the investigation of other parameters, such as higher susceptibility of these patients for immune-related or hematologic diseases, and assess their eligibility for immunosuppressive or cytostatic therapy if the need arises. The aberrations in granulopoiesis and dysplastic changes resembled changes seen in conditions like myelodysplastic neoplasms or myelodysplastic/myeloproliferative neoplasms. These changes can be attributed to hyperinflammation or cytokine release.[17,38] The presence of these dysplastic cells in the blood can jeopardize the host immunity and may lead to secondary infections in these patients. A larger study of COVID patients with secondary infections can help to validate the utility of peripheral smear examination as a potential tool to assess the susceptibility of these patients to secondary infections. This could also help triage patients needing prophylactic antibiotics.[39,40]

Table 3. Summary of the Morphologic Findings of Red Blood Cells (RBC), White Blood Cells (WBC), and Platelets

Cell Type	Significant Findings
Red Blood Cells	Anemia, nucleated red blood cells, schistocytes
White Blood Cells	
Neutrophils	Neutrophilia, toxic granulations, pyknosis, hypo segmentation, hyper segmentation, Pelger-Huet forms
Lymphocytes	Lymphopenia, reactive lymphocytes including Downey forms and plasmacytoid cells/"covidocytes," smudge cells, apoptotic cells, and large granular lymphocytes
Monocytes	Monocytosis, monocytopenia, increase in monocyte size, cytoplasmic vacuolation
Eosinophils	Decrease in eosinophils, cytoplasmic vacuoles
Platelets	Thrombocytopenia, thrombocytosis, both thrombocytosis and thrombocytopenia, giant forms, large forms, platelet clumps or aggregates, platelet satellitism, giant forms with clumping, large, hyperchromatic, vacuolated forms

Many studies reported lymphopenia. Several mechanisms have been postulated for lymphopenia in COVID (42 studies?), including direct infection of T-lymphocytes due to expression of the ACE2 receptor on them, resulting in lymphocyte death,[41,42] and direct viral damage to the thymus and spleen resulting in acute lymphocyte decline.[41] Other studies have postulated that disordered inflammatory cytokines (tumor necrosis factor α, interleukin 6)[41,43] and metabolic molecules elevated blood lactic acid levels can lead to lymphocyte depletion.[41,44] Reactive or atypical lymphocytes are known to be seen in viral infections of various etiologies, such as Epstein-Barr virus, dengue virus, and SARS virus, and recently have been reported in COVID-19 as well with a relatively higher occurrence than seen with previous SARS.[11,27] Downey type II reactive lymphocytes and plasmacytoid forms are reported frequently in various studies and maybe a helpful diagnostic feature, although they are nonspecific and seen in many other conditions.[7,45]

Numerous studies have tried to link the clinical application of lymphocyte morphology or lymphocyte counts to patient prognosis. Berber et al found that lymphopenia was seen in severely ill patients, and pseudo Pelger-Huet anomaly/mature lymphocytes ratio increased in severely ill patients versus the mild stage group ($P < 0.05$).[6] They also found that at the disease onset, patients with an increased number of lymphocytes and monocytes with vacuoles had a short hospital length of stay. Wang et al found that among COVID-19 patients, severely ill cases had a lower level of total lymphocytes, CD4+ T cells, CD8+ T cells, and B cells than the mildly ill cases.[46] Kubik et al postulated that low counts of "covidocytes" that were essentially reactive and plasmacytoid lymphocytes (ie, 0.3%) were classified as "high risk" for a critical outcome.[25]

Viral infections may be associated with monocytes with vacuoles of the peripheral blood smear. Zhang et al reported morphological and inflammation-related changes in monocytes and reported

an increased number of larger, atypical, vacuolated monocytes not seen in healthy individuals' peripheral blood smear, like those seen by Berber et al.[6,30] There is not enough data suggesting an association of these changes in monocytes with prognosis. Similarly, there is not enough evidence reporting a correlation between eosinophilia or its vacuolization with patient prognosis.

Some well-known viral infections that have been associated with lymphomagenesis include Epstein-Barr virus, human T-lymphotropic virus (HTLV-1), hepatitis C virus, human herpesvirus (HHV-8), and HIV.[47] Although coronaviruses have not been associated with the development of lymphomas, long-term follow-up of COVID-19 patients remains essential.

Some limitations of this review include the heterogeneity of the studies, the predominance of case reports, and large variability in the findings. Most of the studies included did not analyze peripheral blood smear changes by SARS-CoV-2 strains or vaccination status, and, thus, the changes could not be evaluated. As new SARS-CoV-2 strains emerge, there is a need to describe the changes seen in the peripheral blood smear related to these specific strains so that any new or unique changes can be evaluated for diagnostic/prognostic significance. Additionally, prolonged pre-analytical time can alter the morphological features of white blood cells. Changes like cytoplasmic vacuolation, hairy projections, nuclear lobulation, vacuolation, and degeneration are observed in white blood cells due to prolonged time intervals between specimen collection and smear preparation.[48] Another limitation is that the effect of prolonged pre-analytical time on white cell morphology was not evaluated by the studies included, and the morphological findings were reported by an single pathologist and were not confirmed by another pathologist or central review.

CONCLUSIONS

There is a spectrum of findings in the peripheral blood in COVID-19--primarily reactive changes in neutrophils, monocytes, lymphocytes, and platelets. Increased neutrophil/lymphocyte ratio and higher neutrophil counts have been associated with poor prognosis, which could help triage patients, but this needs to be confirmed in larger studies.

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