Received: 22 July 2022 | Accepted: 19 September 2022

DOI: 10.1111/bjh.18489

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

REVIEW

# Coronavirus disease 2019 (COVID-19): Focus on peripheral blood cell morphology

**Gina Zini**[1,2] | **Giuseppe d'Onofrio**[1]

[1]Haematology, Catholic University of Sacred Heart, Rome, Italy

[2]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

**Correspondence**
Gina Zini, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Largo Agostino Gemelli 8, Rome 00168, Italy.
Email: gina.zini@unicatt.it

**Summary**

Numerous studies have shown peculiar morphological anomalies in COVID-19 patients' smears. We searched all the peer-reviewed scientific publications that explicitly reference the cytomorphological alterations on peripheral blood smears of patients with COVID-19. We extracted data from sixty-five publications (case reports, patient group studies, reviews, and erythrocyte morphology studies). The results show that frequent alterations concern the morphology of lymphocytes (large lymphocytes with weakly basophilic cytoplasm, plasmacytoid lymphocytes, large granular lymphocytes). Neutrophils display abnormal nuclei and cytoplasm in a distinctive cytomorphological picture. Besides a left shift in maturation, granulations can be increased (toxic type) or decreased with areas of basophilia. Nuclei are often hyposegmented (pseudo-Pelger-Huët anomaly). Apoptotic or pycnotic cells are not uncommon. Monocytes typically have a large cytoplasm loaded with heterogeneous and coalescing vacuoles. Platelets show large and giant shapes. The presence of erythrocyte fragments and schistocytes is especially evident in the forms of COVID-19 that are associated with thrombotic microangiopathies. Such atypia of blood cells reflects the generalized activation in severe COVID-19, which has been demonstrated with immunophenotypic, molecular, genetic, and functional methods. Neutrophils, in particular, are involved in the pathophysiology of hyperinflammation with cytokine storm, which characterizes the most unfavorable evolution.

**KEYWORDS**
blood morphology, COVID-19, lymphocytes, monocytes, neutrophils, platelets

## INTRODUCTION

The first descriptions in the scientific literature of infection by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), referred to as coronavirus disease 2019 (COVID-19), date back to early 2020.[1] Within a few weeks, the first reports of haematological abnormalities were published in different phases of the disease.[2] These first

**Abbreviations:** CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; CPD, cell population data; EBV, Epstein–Barr virus; EDTA, ethylenediamine tetra-acetic acid; FBC, full blood count; Hb, haemoglobin; HIV, human immunodeficiency virus; ICSH, International Council for Standardisation in Haematology; ICU, intensive care unit; IL, interleukin; LGL, large granular lymphocyte; MPO, myeloperoxidase; NET, neutrophil extracellular trap; NRBC, nucleated red blood cells; PB, peripheral blood; PPH, pseudo-Pelger-Huët; RBC, red blood cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura; WBC, white blood cell.

observations were confirmed by studies of numerous patients with COVID-19.[3–5] At this point, 2.5 years after the start of the pandemic, there is now in-depth knowledge of the haematological alterations characteristic of the infection, of their frequency in disease of different severity and requiring a different level of care (intensive care vs. non-intensive care), and of the evolution in the different phases of the disease, up to recovery or death,[6,7] including long-term alterations in recovered patients.[8] Some clinical correlations and their potential value as a more or less unfavourable prognostic indicator of evolution are well established for some anomalies.[9,10]

Quantitative abnormalities of haematological variables measured in the full blood count (FBC) have been described in early works on large COVID-19 patient groups[3] and have recently been updated with new controlled studies[5,9,11] and reviews.[7,10,12] In most cases, anaemia is absent, mild or moderate, and, in pathogenetic terms, of the hyporegenerative form usually associated with inflammatory and infectious diseases. Anaemia can be more severe in COVID-19 cases with microangiopathic and haemorrhagic complications from disseminated intravascular coagulation. In these same patients, platelet counts, which are otherwise often normal, can also decrease markedly. The occasional anaemia and thrombocytopenia can have prognostic implications. The more consistent abnormality of white blood cells (WBCs) is lymphocytopenia, which is frequent in all hospitalised patients and, differing from $CD4^+$ lymphocytopenia of human immunodeficiency virus (HIV) infection, does not involve a specific subpopulation but rather all lymphocyte subsets to an often indistinguishable extent.[13,14] Infection and destruction of lymphocytes by the virus (apoptosis) are likely to cause lymphocytopenia. On the other hand, the absolute number of circulating neutrophils is higher in the most severe and protracted forms of the condition. Neutrophilia in severe cases is one of the most distinctive haematological aspects of COVID-19, which distinguishes it from most other respiratory viral infections and is part of the context of the hyperinflammatory syndrome with cytokine storm that occurs in severe COVID-19 cases.[15]

Alongside those above haemocytometric and quantitative alterations, it is now an established fact that the cells that circulate in the peripheral blood (PB) of many patients with COVID-19, especially in the clinically relevant forms observed in intensive care units (ICUs) and non-ICU hospital settings, show evident morphological alterations, more marked and more common than those observed in other viral and, more generally, infectious diseases.[4,12] Our review focusses on the literature explicitly dealing with qualitative morphological features of PB circulating cells in patients with COVID-19 to collect all the available information and highlight the most frequent and, if it is the case, characteristic morphological features of any type of such populations.

We wanted to know: (i) whether published studies have described consistent morphological anomalies in cells on the PB film of patients with COVID-19; (ii) if any such abnormalities could be considered typical and have diagnostic or prognostic value in the context of COVID-19 clinical evolution; and (iii) if any of the morphological findings could be ascribed to a relationship with the physiopathological events that characterise the different evolutionary patterns of COVID-19 (i.e., cytokine storm, respiratory distress, thrombosis and microangiopathy).

In our literature study, we searched the keywords referring to all blood cells and their qualitative alterations in any possible combinations on the PubMed and Google Scholar databases with the search terms 'COVID-19' and 'SARS-CoV-2'. We included in the study all peer-reviewed publications describing specific morphological aspects of blood cells. We excluded the pre-print and a few other papers in which, in our opinion, the minimum requirements were not met in terms of diagnostic criteria.

## Types of studies

We have included in our literature review a total of 65 studies published from March 2020 until June 2022, which describe the morphological alterations of circulating cells in the PB film of patients with COVID-19. Among these, there were 15 case reports dealing with morphological aspects. Four case reports limited the cell anomaly descriptions to lymphocyte abnormal morphology.[16–19] One of them had a clonal CD5-negative B-cell lymphocytosis[18]: the authors highlighted an excess of smudge cells in the films. In a recent report, a case of $CD5^+$ monoclonal B-cell lymphocytosis was diagnosed at the time of the first SARS-CoV-2 positive test[20]: the clonal lymphocytes showed rod-shaped crystals in their scanty cytoplasm. In another six case reports, the authors extended their observation to neutrophils and monocytes,[21–26] and three reported a leucoerythroblastic picture,[27,28] with abnormal monocytes in one case.[29] One study describes a transitory reversible increase in circulating and bone marrow blast cells during COVID-19.[30] Several reports of COVID-19 in patients with coinciding or pre-existing haematological disorders were also available, in which no COVID-19 PB morphology was considered and that had no specific relevance for our morphology focused review.

We found 28 studies dealing with morphological alterations observed in groups of multiple COVID-19 patients. Nine reported atypia of a single cell population: abnormal lymphocytes in seven,[31–37] atypical monocytes in one.[38] In all, 19 of these group studies detailed morphological abnormalities in multiple cell populations in patients with different phases of the disease (10 of them included control groups of healthy subjects or patients with non-COVID-19 inflammatory states) (Table 1).[11,39–56] Other studies described case reports or original articles specifically dedicated to red blood cell (RBC) morphological abnormalities, with particular reference to the presence of schistocytes in COVID-19-related microangiopathies (subsection 'Red blood cells').

Besides several reviews limited to quantitative FBC data in COVID-19,[10,57,58] five reviews on haematological features

**TABLE 1** Summary of peripheral blood morphological findings in the studies with the description of multiple cell line abnormalities

| Reference | COVID-19 positive | COVID-19 negative | Neutrophil cytoplasm | Neutrophil nucleus | Lymphocytes | Monocytes | Platelets | Other |
|---|---|---|---|---|---|---|---|---|
| Zini et al.[39] | 40 | | Toxic granules, blue areas | Hyposegmented, PPH, apoptotic | Heterogeneous (large, lymphoplasmacytoid, increased LGL | - | Large, hyperchromic pseudopods | Immature granulocytes |
| Sadigh et al.[40] | 27 | 14 | - | Smudge granulocytes, left shift | Atypical, plasmacytic, circulating plasma cells | - | Large, giant forms | NRBCs |
| Lüke et al.[41] | 45 | - | Hypergranular | PPH, apoptosis | Multilobed, lymphoplasmacytoid, LGL | Aberrant, clumped chromatin, basophilic cytoplasm | Anisocytosis, giant forms, aggregates | Stomatocytosis, rouleaux, target cells, basophilic stippling, NRBC |
| Nazarullah et al.[42] | 12 | 10 | Toxic granules, vacuoles, Döhle bodies (<10%) | PPH (non-lobated), apoptosis | Atypical, large clear cytoplasm, plasmacytoid | - | - | NRBCs, blasts (1 case) |
| Singh et al.[43] | 50 | | Toxic, coarse granules, hypogranularity, vacuoles | Hypolobation, dyspoiesis, left shift | Variant, plasmacytoid, blastoid, intranuclear inclusions, increased LGL | Vacuolation, granules, haemophagocytosis | Giant forms | |
| Schapkaitz et al.[44] | 102 (25 ICU) | 21 HIV+ | Hypogranular | PPH, apoptotic chromatin, left shift | Atypical, large cytoplasm, plasmacytoid, increased LGL, pleomorphic, lobulated, vacuoles | - | Large and giant forms | Immature granulocytes, NRBCs, RBC fragments (11.8%) |
| Nath et al.[45] | 26 paediatric | - | Toxic granules, hypogranular, vacuoles | Hypolobation, ring shape, apoptosis, karyorrhexis | Atypical, plasmacytoid, monocytoid, increased LGL | Abnormal morphology | Large, giant, hyperchromatic forms | |
| Ahnach et al.[46] | 15 | - | Hypogranular | Hyposegmentation | Activated | Large | Giant forms | Eosinophil vacuoles |
| Berber et al.[47] | 40 (24 mild, 26 severe) | 30 healthy subjects | Toxic granules or hypogranular, some vacuoles, basophilic stain | PPH, increased bands, karyolysis, karyorrhexis | Atypical, Downey-like, some blast-like | Vacuolisation, sometimes severe | Large, hyperchromic, pseudopods | Immature granulocytes |
| Pozdnyakova et al.[11] | 90 (51 ICU) | 30 (ICU patients) | Toxic granules (97%), vacuoles, Howell-Jolly-like inclusions, Döhle bodies | Left shift | Atypical, plasmacytoid, vacuoles, increased LGL | Large, coalescing vacuoles | | Eosinophil vacuoles, immature granulocytes, NRBCs (in ICU) |
| Gabr et al.[48] | 113 | 50 | Hypogranular, toxic granules | PPH, defective segmentation, hypercondensed chromatin, pyknosis, karyorrhexis | Reactive, vacuolated, plasmacytoid, bizarre nuclear shape, pseudopods, Mott cells | Abnormal, reactive, vacuolated | - | Smear/smudge cells |
| Horiuchi et al.[49] | 40 (26 mild, 14 severe) | 38 | Hypogranular, toxic granules, Döhle bodies, vacuoles (95%), giant forms | PPH, abnormal chromatin | Reactive, vacuoles, increased LGL | | | Polychromasia, schistocytes |
| Alnor et al.[50] | 74 | 228 | Hypogranular ($p < 0.001$) | - | Activated (more frequent in non-COVID-19 ICU patients) | - | (increased MPV and PDW) | Immature granulocytes |
| Kaur et al.[51] | 20 | - | Toxic granules, vacuoles | PPH, abnormal shapes | Large blue cytoplasm, lymphoplasmacytoid, increased LGL, Mott cells | Activated, abnormal shapes, vacuolisation | | Immature granulocytes, smudged neutrophils, a few NRNC, basophilic stippling, platelet clumping |

(Continues)

**TABLE 1** (Continued)

| Reference | COVID-19 positive | COVID-19 negative | Neutrophil cytoplasm | Neutrophil nucleus | Lymphocytes | Monocytes | Platelets | Other |
|---|---|---|---|---|---|---|---|---|
| Pezeshki et al.[52] | 89 | - | | Left shift | Atypical, increased LGL | | Giant forms | Smudge cells (67.4%), schistocytes, immature granulocytes, NRBCs |
| Refaat et al.[53] | 19 (no cancer) 84 (cancer) | 30 (healthy) | Toxic granules | PPH, (bilobed, dumbbell), coarse chromatin | Plasmacytoid, reactive (ballerina-like), covicytes (see text) | Aggressive-looking, giant size, vacuoles | | Increased RDW, decreased eosinophils, granulocyte left shift |
| Jain et al.[54] | 80 | 32 | Toxic granules, vacuoles | Hypersegmentation, PPH, non-lobated, ring-shape | Reactive (increased in fatal cases), lymphoplasmacytoid | Vacuoles (increased in fatal cases) | | Granulocyte left shift, smudge and apoptotic neutrophils, NRBC, schistocytes |
| Singh et al.[55] | 100 (50 ICU) | - | Toxic granules, vacuoles | PPH (50% in ICU cases), hypolobation, karyolysis | Plasmacytoid, Downey cells, hyperbasophilic cytoplasm, pseudopod formation | Cytoplasmic vacuoles and granules | Large, giant, pleomorphic (ICU patients) | Apoptotic bodies, karyorrhexis |
| Zini et al.[56] | 77 | - | Hypergranular, hypogranular, pale blue areas, frequent partial MPO deficiency | PPH, hypercondensed chromatin | Activated | | | NRBC, immature neutrophils, occasional pyknotic and smudge cells |

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; ICU, intensive care unit; LGL, large granular lymphocyte; MPO, myeloperoxidase; MPV, mean platelet volume; NRBC, nucleated red blood cell; PDW, platelet distribution width; PPH, pseudo-Pelger-Huët anomaly; RDW, red cell distribution width.

of the PB in COVID-19 include variably extended cytomorphological information.[4,7,12,59,60] Other literature reviews were dedicated specifically to eosinophils,[61] RBCs,[62] and the association of thrombotic thrombocytopenic purpura (TTP) with COVID-19 or anti-COVID-19 vaccination.[63]

## MATERIALS AND METHODS

In general, the authors used optical microscopes and manually spread PB films fixed and stained according to Romanowsky panoptical methods (May-Grönwald-Giemsa, Giemsa, Wright-Giemsa or Leishman-Giemsa). Among all the studies, nine used automatically spread and stained films processed with digital image analysers.[11,16,18,35,38,40,42,49,50]

All cell images in Figures 1–3 of this review were taken by the authors of this review from May-Grünwald-Giemsa fixed and stained PB films using a Zeiss photo camera and microscope using a ×100 oil-immersion objective.

## PERIPHERAL BLOOD CELL MORPHOLOGY IN COVID-19

### Lymphocytes

Lymphocytopenia is frequent in COVID-19 on admission,[2] and its severity is associated with unfavourable progression. It was described from the beginning of the COVID-19 pandemic in China, with a high proportion in patients admitted to hospital.[1] The decrease in circulating lymphocytes is generally more severe in patients requiring assisted respiration and in ICU patients and is more marked in cases with unfavourable evolution[11]: Pozdnyakova et al.[11] demonstrated a continuing decline in the absolute lymphocyte count from ICU admission to demise. All $CD3^+$ T-lymphocyte subsets and B lymphocytes were reduced, especially in severe cases,[13,14,42,64,65] although the loss of $CD8^+$ lymphocytes was predominant in some studies (Figure 1).[65]

The presence of lymphocytes with abnormal morphology is a universal finding in blood films from SARS-CoV-2-infected patients, even in the context of lymphocytopenia. It is reported in almost all morphological studies and considered heterogeneous by their authors. Such lymphoid cells are generically defined as atypical,[11,40,45,47,52] reactive,[16,22,37,48,49] activated,[46,50] variant[21] or pleomorphic,[25,44] and are similar to those seen in Epstein–Barr virus (EBV) and cytomegalovirus (CMV),[25] and other viral infections.[11] Such terminology variability and confusion is reflected in the PB cell nomenclature document published by the International Committee for Standardization in Haematology (ICSH).[66] The ICSH recommends that '*reactive lymphocytes* is used to describe lymphocytes with a benign aetiology, and *abnormal lymphocyte* with an accompanying description of the cells is used to describe lymphocytes with a suspected malignant or clonal aetiology'. According to the European

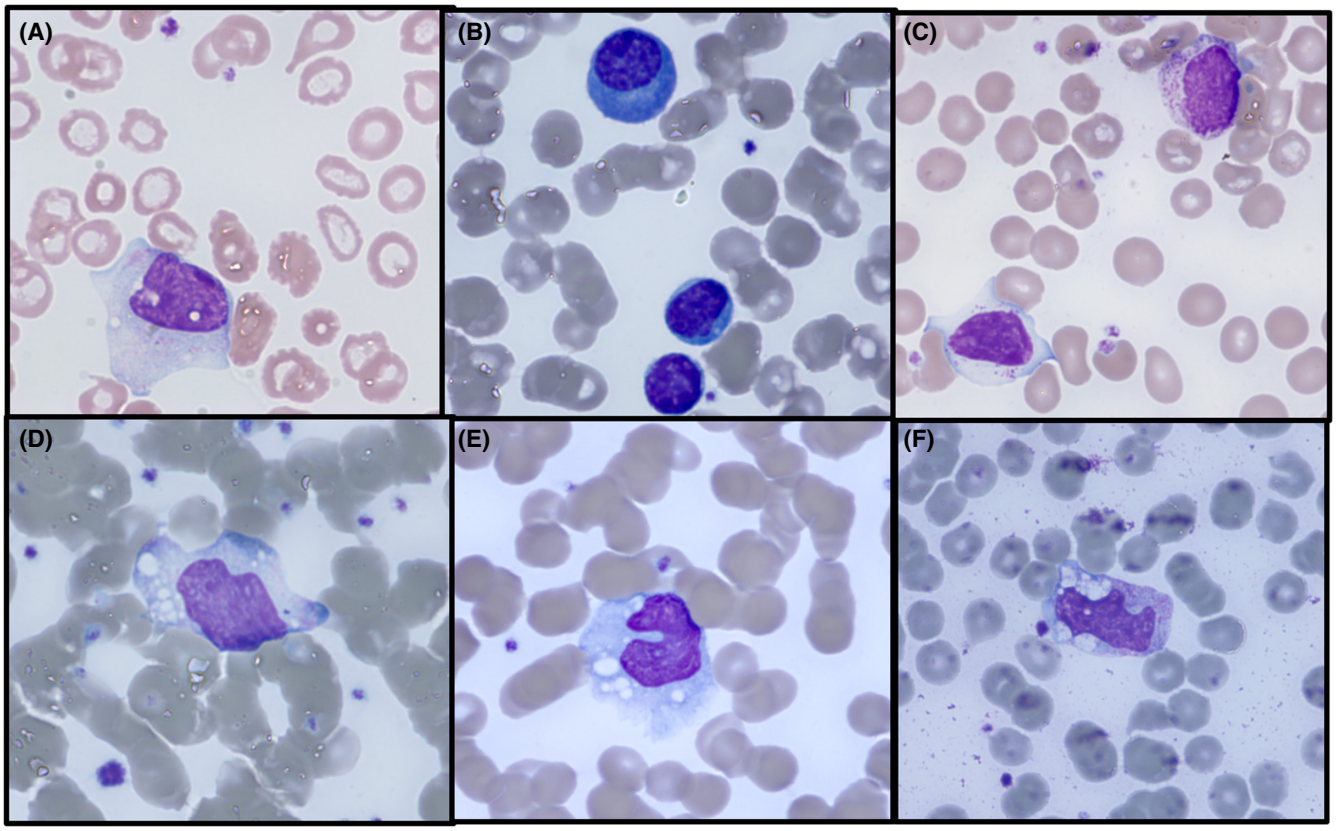


**FIGURE 1** Lymphocytes and monocytes from peripheral blood films of patients hospitalised with coronavirus disease 2019 (COVID-19). (A) A large lymphocyte with voluminous cytoplasm, light blue, containing very fine azurophilic granules and a rounded vacuole. The edge of the cytoplasm is deformed by the surrounding red blood cells. The eccentric nucleus has an irregular profile with small notches and contains a perfectly round vacuole. Chromatin is distributed in heterogeneous condensation zones separated by lighter spaces. The general morphology is similar to a Downey type II cell of infectious mononucleosis. Above, to the right, is a teardrop cell or dacrocyte. (B) In the upper part, a circulating plasma cell with intensely basophilic cytoplasm, eccentric round nucleus with blue chromatin, and clear perinuclear sarcoplasm. Below are two small lymphocytes, the larger of which has intensely basophilic cytoplasm. (C) Bottom left a large granular lymphocyte (LGL). The cytoplasm is clear, with a slight peripheral increase in basophilia, and contains about 20 distinct dark red granules (note the difference from the fine azurophilic granules in (A). In the upper right corner is a granulocyte precursor with an oval nucleus, granular chromatin, and several small nucleoli. The granules appear mature, and a clear paranuclear area corresponding to the Golgi apparatus is not visible (nucleus-cytoplasmic maturation asynchronism). (D) A monocyte of intermediate appearance, spongy nuclear chromatin, and fine nucleoli. The nuclear profile is moderately irregular, with multiple shallow notches. The cytoplasm is greyish-blue, with numerous vacuoles of heterogeneous size. The peripheral accentuation of the staining is due to the superposition of the cytoplasm on the surrounding red blood cells, which do not easily deform the external profile of the monocyte. Note a sizeable hyperchromatic platelet at the bottom left of the image. (E) A monocyte with voluminous light blue cytoplasm pierced by multiple vacuoles of heterogeneous size and variable shape, round or ovoid. The nucleus is C-shaped. (F) A monocyte with greyish cytoplasm full of violet granules and, on the left side, fully occupied by numerous coalescing nucleoli.

LeukemiaNet nomenclature, abnormal lymphoid cells should be respectively named 'atypical lymphocytes, suspect reactive' and 'atypical lymphocytes, suspect neoplastic'.[67] However, in this review we have exactly reported the atypical lymphoid terminologies originally adopted by the authors, which gives a further impression of the confusion in this area. If not otherwise specified, all the abnormal lymphoid cells in patients with COVID-19 are 'reactive lymphocytes' according to the ICSH and 'atypical lymphocytes, suspect reactive' according to LeukemiaNet.

Thus, in patients with COVID-19, the following three morphological subtypes have been reported with high frequency:

1. Large lymphocytes with increased amounts of pale or more intensely blue cytoplasm are common[25,39,42,51]: these cells are often deformed by the adjacent RBCs, an aspect colourfully nicknamed 'ballerina skirt appearance',[19,53] or identified with Downey type II cells or Downey type III immunoblasts of infectious mononucleosis.[36,42]
2. Lymphoplasmacytoid cells, with an eccentric nucleus, plentiful deep blue basophilic cytoplasm and perinuclear hof (halo), are mentioned by almost all authors. Reports of circulating plasma cells are less frequent[48] and include a minority with plasmablastic features (immature chromatin and nucleoli).[31] Mott cell-like plasmacytoid lymphocytes, with prominent immunoglobulin cytoplasmic inclusions, or Russell bodies, are also mentioned.[17,19,48,51]
3. The proportion of large granular lymphocytes (LGLs) without substantial morphological atypia is reported to be increased in almost all papers.

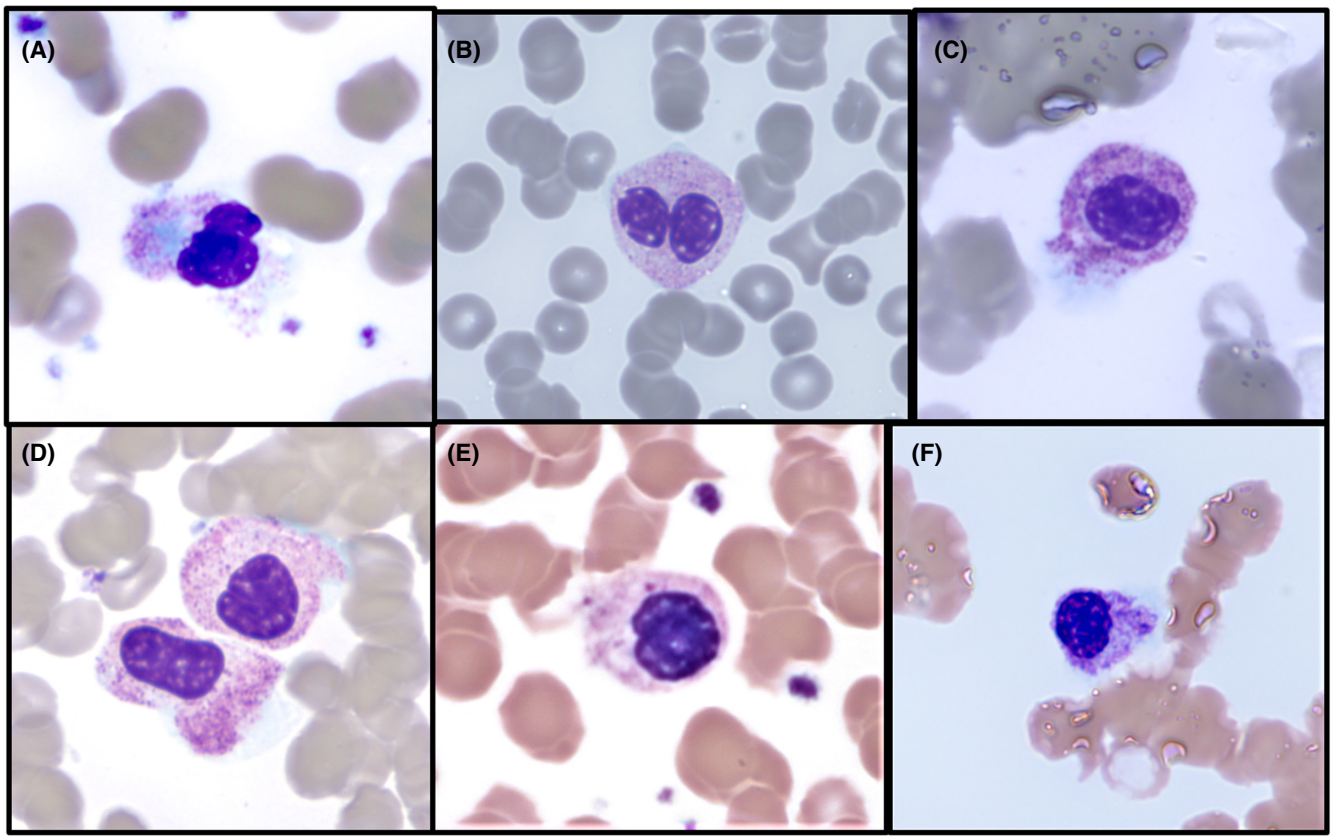


**FIGURE 2** Neutrophils from peripheral blood films of patients hospitalised with coronavirus disease 2019 (COVID-19). (A) A neutrophil with strongly condensed nuclear chromatin. The cytoplasm shows toxic granulation and an irregular area of intense basophilia close to the nucleus. The right side of the cytoplasm has a frayed edge. (B) A neutrophil with a bilobed nucleus, pseudo-Pelger-Huët type. (C) A neutrophil with toxic granulation and an inferior border of ragged and basophilic cytoplasm. The unlobed nucleus has a polycyclic outline. (D) Two neutrophils with unlobed nuclei (pseudo-Pelger-Huët). (E) A neutrophilic with an unsegmented nucleus with strongly condensed pre-apoptotic chromatin and hypogranular cytoplasm. (F) A neutrophil with a unlobed nucleus with very compact chromatin and sparse cytoplasm with purplish granules and a basophilic halo on the right.

Additional morphological features mentioned by several authors among the atypical features of the COVID-19 lymphoid populations are:

1. Cytoplasmic vacuoles[11,35,48,49]
2. Cytoplasmic basophilia, generalised[36] or confined to cytoplasmic margins[25]
3. Lobulated nuclei[41,44] or bizarre nuclear shape
4. Spongy[35] or loose[36] chromatin and presence of a nucleolus,[25,35] similar to blasts[25,30]
5. Apoptotic lymphocytes, with an amorphous mass of chromatin[21,25,39]
6. Presence of pseudopods[21,48,53,55]
7. Smudge or smear cells, considered of lymphoid origin[18]

Refaat et al.[53] described a COVID-19-specific presence of a particular type of abnormal lymphocyte they named 'covicyte', characterised by clumped nuclear chromatin and deep-blue cytoplasm with a granular tail; the presence of such cells would be associated with a better prognosis.[45,53] A few authors have used generic and imprecise definitions, such as monocytoid,[45] Downey-like,[47] blastoid,[21] or blast-like cells.[47] Only one paper mentioned the presence of intranuclear inclusions in lymphoid cells.[21]

The number and proportion of atypical lymphoid cells out of the whole lymphocyte population were described as highly variable in the different papers and in the different patients, but it was higher, with one exception, compared to the control population when such was available. In one study, atypical lymphocytes were present in 16% of patients at the first visit, while the median time for their appearance in most patients was 8 days, with a peak at day 9.[37] In a reported multivariate analysis, the presence of atypical lymphocytes, especially with lymphoplasmacytic features, was predictive of COVID-19 positivity,[11] or was found to be valuable as an indication for reverse transcriptase polymerase chain reaction for SARS-CoV-2.[68] In only one study, was the proportion of atypical lymphocytes higher in non-COVID-19 ICU patients than in patients with COVID-19.[50] Interestingly, according to some authors, the presence of[35] or an increase in[37] circulating atypical lymphoid cells was associated with better prognosis and favourable evolution. In contrast, according to others, atypical lymphocytes were characteristic of the initial stages or milder forms,[11] or were not related to the severity of the disease.[36]

Atypical lymphocytes were also observed in bronchoalveolar lavage fluid[36,69] and in pleural fluid.[70]

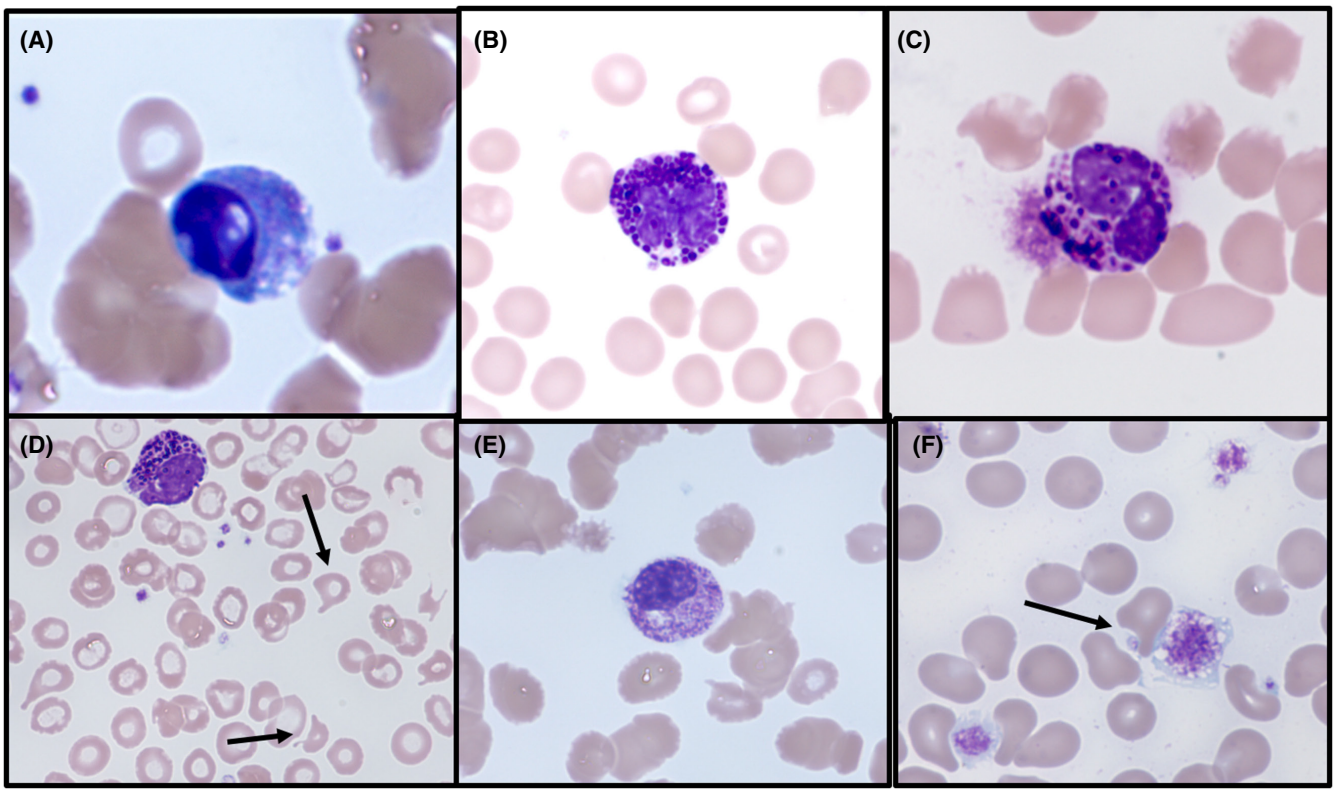


**FIGURE 3** Various cells from peripheral blood films of patients hospitalised with coronavirus disease 2019 (COVID-19). (A) Circulating apoptotic cell. Note the unstructured, amorphous nuclear chromatin and the intensely basophilic cytoplasm containing granules and vacuoles. It could represent a neutrophil but also possibly a lymphocyte or monocyte. (B) A basophil with clearly evident numerous granules, partly overlapping the nucleus: The morphology is generally normal. (C) Dysmorphic eosinophil metamyelocyte, with coarse red-blackish granules (pro-eosinophilic) superimposed on the eosinophilic granules, visible particularly near the nucleus. (D) Above, a normal-looking basophil. In the erythrocyte population on the right side of the image, several schistocytes can be seen, some of them with the typical shape of keratocytes (arrows). On the left, a dacrocyte. (E) Around a small neutrophilic myelocyte, several small agglutinates of red blood cells are seen, likely reflecting the presence of autoantibodies. (**F**) A giant platelet, rich in vacuoles, and two large platelets, in which the distinction between the central granulated part (chromomer) and the peripheral basophilic part (hyalomer) is visible.

## Neutrophil granulocytes

Neutrophilia is not rare in COVID-19[10] and is a sign of adverse prognosis.[4,6,39,71] Neutrophil counts tend to be increased in patients admitted to ICUs and in fatal cases of COVID-19.[72] Given the quantitative changes concerning the two main circulating leucocyte classes, it is not surprising that an increased neutrophil/lymphocyte ratio has been identified as a significant predictor of prognosis and survival in patients with COVID-19.[73,74]

Many authors have described morphological abnormalities in neutrophil granulocytes. In most cases described with sufficient details, neutrophil dysmorphism were associated and more marked in the not rare cases with absolute neutrophilia and severe diseases, progressing toward respiratory failure (Figure 2).[42]

Generic definitions, such as dyspoiesis[21] or dysplasia,[22,48] have sometimes been used. The literature review showed that neutrophil abnormalities were often reported as striking and showed a high degree of consistency, so it is possible to delineate a COVID-19-typical combination of neutrophil aberrations involving the nucleus and cytoplasm. The abnormal features described below, heterogeneously associated in variable combinations, are typically described in PB films of patients with COVID-19. We have recently shown that the vaccination status does not have any substantial effect on the frequency, type or severity of morphological abnormalities is COVID-19 hospitalised patients.[56]

### Neutrophil cytoplasmic abnormalities

1. Hypergranular cytoplasm (dark, crowded, coarse, «toxic» type), often reported as toxic,[24,26,39,41–43,45,47–49,51] found in up to 97% of patients.[11]
2. Hypogranular cytoplasm.[26,39,43–50] Not uncommonly a combination of hypergranular/toxic neutrophils with hypogranular neutrophils on the same film is reported.
3. Presence of small basophilic, agranular cytoplasmic areas, blue areas or Döhle bodies[11,39,42,47,49,54]; such pale blue areas correspond to membranes of the endoplasmic reticulum.
4. Cytoplasmic vacuoles,[11,43,45,47,51,55] found in up to 95% of cases.[49]
5. Blue-green cytoplasmic inclusions (ascribed to lipid-rich lipofuscin from necrotic liver cells), observed in severe or fatal cases.[24,47]

6. Decreased myeloperoxidase (MPO) activity using automated cytochemistry blood cell counters.[56]

### Neutrophil nuclear abnormalities

The most frequent findings are nuclear hyposegmentation or absence of nuclear lobation, with dark clumped chromatin[4,39,43,45,46,48] and unusual nuclear profiles (rounded, C-shaped, fetus-like or ring-shaped).[45,54] The nuclear hyposegmentation with abnormal,[49] hyperdense[48] or amorphous[39] chromatin is often referred to as acquired or pseudo-Pelger-Huët (PPH) anomaly: a similar morphology is reported in COVID-19 by the majority of authors.[21,22,39,41,42,44,47–49,51,54] In one study of 12 patients, PPH anomaly was found in all COVID-19 cases, with 50% having over 10% of 'pelgeroid' neutrophils and 50% having neutrophils with non-lobated nuclei.[42]

In addition, the following nuclear shapes or structural abnormalities have been variably reported:

1. Hypersegmented nuclei[26]
2. Detached nuclear fragments,[21] also indicated as Howell–Jolly body-like inclusions[11]
3. Karyorrhexis[45,47,48]
4. Karyolysis[47,55]

### General neutrophil abnormalities

1. Apoptotic neutrophils in the circulation,[4,25,39,41,44,45,55] also referred as pyknosis[48]
2. Disintegrated or smudged neutrophils[48]
3. Giant forms[49]
4. Myeloid left shift,[11,21,44,52] almost universally present, with an increased proportion of band forms[39,52] and circulating granulocyte precursors, such as metamyelocytes, myelocytes, promyelocytes and even blasts with cytoplasmic granules.[27,39–41,50–52] They occasionally combine with circulating nucleated RBCs (NRBCs) in a leucoerythroblastic picture (see below and Table 1).

## Monocytes

Monocytes are numerically neither increased nor decreased. According to most reports,[38] although monocytopenia and depletion of specific monocyte subsets have been described.[75,76] However, the majority of studies have reported the presence of monocytes with atypical, aberrant shapes in the PB film of patients with COVID-19,[41,45] not seen in the circulation of healthy individuals and not expected, with the same consistency, in other viral or bacterial infections. Differently from the pleomorphism of the COVID-19 atypical lymphocyte populations described above, the atypical monocytes in COVID-19 appear to have relatively consistent morphological features. In particular, they are larger than usual.[38,46] Using automated blood cell counters, the value of the monocyte volume distribution width is increased, indicating an increased volume heterogeneity.[76,77]

In general, monocytes maintain their abundant greyish-blue cytoplasm and fine cytoplasmic granulations, but basophilic cytoplasm and clumped chromatin[41] and increased cytoplasmic granules have been occasionally reported.[43,55] An impressive morphological monocyte feature, highlighted by almost all authors, is an increase and dysmorphism of cytoplasmic vacuolisation, considered striking in some studies, with many large coalescing empty vacuoles.[11,21,29,38,47,48,54] Sporadic cases with haemophagocytosis images in PB have been described.[21] Blue-green cytoplasmic inclusions, similar to those observed in neutrophils, have been seen in fatal cases.[24]

Some authors consider COVID-19 monocytes to be activated[21,51] or reactive[48] based on their morphological features. In effect, functional changes, with an increase of activation and inflammation markers, have been reported in COVID-19 monocytes.[38,68] In one study, monocyte size was significantly and positively correlated with the expression of the pro-inflammatory marker interleukin (IL)-8.[68]

## Eosinophil granulocytes

There is significant heterogeneity of results for possible quantitative variations of eosinophils in COVID-19: eosinophil number and morphology have not been reported among the most frequent and substantial blood cell alterations in these patients. Several authors reported normal eosinophil count or eosinopenia; eosinophil count tends to be low in patients admitted to hospital and ICU and in fatal cases of COVID-19.[61,78,79] One study showed a correlation between eosinophil and lymphocyte counts, except for patients with severe disease on the first day after hospital admission who had low values for eosinophils.[78] Apart from a few isolated reports, eosinophilia is not a characteristic of COVID-19. In a study on 314 cases, 28.7% at admission had mild eosinophilia ($0.5–1.5 \times 10^9$/L), which increased during the first week of treatment: such patients with eosinophilia had lower C-reactive protein and lower requirement for hospital stay, ICU admission, mechanical ventilation, and oxygen supplementation (milder clinical course and better disease outcome) so that a protective role of eosinophils in mitigating the severity of inflammation was suggested.[80]

From a morphological point of view, on the other hand, we have found very few reports of eosinophil abnormalities, such as 'dysmorphisms' (trilobed or unsegmented nucleus, hypogranular cytoplasm, multiple vacuoles).[11,23] Atypical immature eosinophils can be occasionally seen (Figure 3).

## Basophil granulocytes

Chen et al.[81] found that the absolute count of basophils in patients with COVID-19 was lower than in the control group but higher than in patients with influenza. No morphological details about basophil abnormalities are available in the reviewed literature (Figure 3).

## Leucoerythroblastic picture

The presence of NRBCs in the circulation, usually combined with metamyelocytes, myelocytes or promyelocytes, was initially observed in 1% of 300 patients by Buoro et al.[82] at the beginning of the pandemic in Italy and confirmed in early case reports.[27,28] Recent studies on groups of patients reaffirm such a finding,[40,41,44,50,51] in some reports with higher frequency in patients requiring intensive support.[11] The circulating NRBCs can show dyserythropoietic features.[29] A circulating megakaryocyte was reported in a single case.[29]

## Blast cells

Rare circulating blasts have been occasionally reported.[25,42] A transient increase in blast cell count to 6%, mimicking acute leukaemia, was described in a single COVID-19 case.[30] The bone marrow aspirate was hypocellular with 23% blasts and decreased proportion of granulocytes with left shift. PB and bone marrow reverted to a normal picture with no blasts after 2 weeks.

## Red blood cells

Anaemia in COVID-19 is often absent or mild at presentation. Median haemoglobin (Hb) at concentration on admission in the low normal range was reported in a large group study.[5] The Hb tends to decrease with disease progression. In a group of 259 hospitalised patients, anaemia was mild in 14%, moderate in 8.1%, and severe in only five (1.9%); the percentage of anaemic patients increased to 68.8% 1 week after admission; moderate or severe anaemia was associated with more extended hospital stay and poor survival.[83]

If present, anaemia is usually of the normocytic normochromic type, with no abnormalities of mean cell volume, mean cell Hb or mean cell Hb concentration in the absence of associated iron or vitamin deficiencies or Hb disorders. However, increased anisocytosis is commonly reported, and an increase of the automated index of anisocytosis, the red cell distribution width, measured by modern blood cell counters, has been confirmed as a reliable, although nonspecific, marker of worse prognosis.[84–86]

On the other hand, RBC shape abnormalities have only occasionally been reported; these have included polychromasia,[49] basophilic stippling,[29,41,51] dacrocytes,[28] stomatocytosis, increased rouleaux formation,[41] and RBC fragments/schistocytes.[44,49,52] In a study of 20 patients with COVID-19 in the ICU or sub-ICU from Northern Italy, a peculiar picture of polychromasia, basophilic stippling, rouleaux formation and autoagglutination has been described and considered compatible with autoimmune haemolytic anaemia[87]; spherocytes and knizocytes (with a doubled or tripled or variably shaped pale central ridge) were also present and the direct antiglobulin test was positive in 50%.

The presence of schistocytes (Figure 3) has been observed in patients with thrombotic microangiopathy or TTP occurring as the initial presentation of COVID-19,[88–90] or in patients with simultaneous or preceding COVID-19 test positivity.[91,92] The presence of schistocytes together with echinocytes and mushroom cells has been described in two patients with acute kidney injury.[93] In one study, the ICSH guidelines for schistocyte microscope evaluation[94] were followed: schistocytes (≥1%) were found in a high proportion of patients with COVID-19,[95] at various stages of the disease and with variable severity, irrespective of lung involvement and overt intravascular coagulation. A moderate increase of schistocytes (2%–4%) was reported in 50 consecutive patients using the Sysmex XN-9000 blood cell counter with microscope confirmation, in association with increased lactate dehydrogenase and D-dimer and mild decrease of A disintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13 (ADAMTS13) activity,[96] a combination that supports the presence of microangiopathy in COVID-19. In addition, schistocytes and TTP have even been observed after anti-COVID-19 vaccination.[63,97–101]

## Platelets

The platelet count has been reported as normal[32] or decreased on admission to hospital.[2,13,102,103] In one of the first clinical descriptions from China, the frequency of low platelet count at admission was 36.2%.[2] The count may change during disease evolution, and patients with severe or critical diseases can have a reduced platelet count.[102] In one study, 45.5% of patients had a count of $<100 \times 10^9$/L.[103]

Platelets are often morphologically abnormal in COVID-19 and can have a hyperactive phenotype.[104,105] The following platelet shape features have been described in patients with COVID-19:

1. Platelet anisocytosis[42] and pleomorphism.[56]
2. Large or giant platelets (Figure 3),[21,39–41,44,52,55] including in children.[46] Using automated blood cell counters, platelets in COVID-19 have an increased mean platelet volume in some studies.[50]
3. Hyperchromatic platelet granulomere (Figure 3).[45,47]
4. Peripheral clear areas of different sizes.[39]
5. Pseudopodial protrusions.[39,47]
6. Platelet clumping or aggregates.[41]

## Full blood count, morphology and clinical correlations

Few studies have determined and reported the percentage of the different circulating leucocytes with morphological abnormalities. In a detailed report of 12 patients with COVID-19, 50% of cases had >10% monolobated neutrophils or PPH on the PB film.[42] Such a finding was observed in five of the seven patients who progressed to respiratory failure but in only one of those with a stable clinical course. Absolute neutrophilia was present in four of the six cases with such a high percentage of PPH neutrophils.

Neutrophil morphological abnormalities are often, but not always, associated with absolute neutrophilia. According to some studies, they are more frequent in ICU than in non-ICU COVID-19 patients.[55] PPH, in particular, like lymphopenia, is described as more frequent ($p < 0.05\%$) in severe stage subjects[47] and patients progressing to respiratory failure. PPH and increased pyknotic and damaged cells have been reported as specific and predictive of the diagnosis of COVID-19 patients compared with patients with non-COVID-19 diseases.[48] In a group of 80 patients with COVID-19 (41 ICU and 39 non-ICU), left myeloid shift, ring-shaped neutrophils, prominence of monocyte vacuolisation, and LGLs emerged as highly sensitive markers of disease severity, so that serial analysis of the PB film potentially predicts the course of the disease. Neutrophil nuclear abnormalities tend to disappear during anti-viral and anti-inflammatory treatment[39] and after elimination of the virus (i.e., after a negative SARS-CoV-2 test).[41] Similarly, toxic coarse cytoplasmic granules, left shift, and apoptotic cells, decrease during follow-up.[45]

Not all studies confirmed statistically significant correlations between morphological neutrophil abnormalities and clinical severity of the disease[46,49,52] or between ICU and ward patients.[48]

The percentage of atypical lymphocytes did not generally correlate with the WBC or the absolute lymphocyte count but was less evident in patients with lymphopenia. Similarly, the proportion of vacuolated monocytes did not significantly affect monocyte count. However, in most studies, a high proportion of atypical lymphocytes of reactive type and monocytes with exuberant vacuolation was associated with initial and milder disease. In COVID-19-positive cases, the presence of monocyte vacuolisation or atypical lymphocytes reduced the odds of being in the ICU by 0.21- and 0.23-fold respectively.[11] These authors used a digital morphological analyser and did not note significant neutrophil nuclear abnormalities in neutrophils but only left-shifted immature granulocytes and vacuolisation with toxic granules in severe cases.[11] Others have confirmed that hospital stay can be shorter in cases with a high initial vacuolated monocyte count.[47] In one study, absolute counts of LGLs and reactive lymphocytes were significantly decreased in the severe cases, while average or higher levels of LGL ratios were present in the milder cases despite the decrease in total lymphocytes; patients who showed an increase in LGLs, even transiently, tended to recover.[49] A LGL increase thus seems associated with an effective immune response and could represent a promising marker in the early screening stage for critical illness and recovery from severe COVID-19.[49] Lymphocyte morphology abnormalities, in other studies, did not show a specific combination with the clinical course of the disease.[42]

## Limitations of the morphological findings

A certain degree of subjectivity is inherent in cell identification and interpretation. All the articles and case reports we reviewed were, however, accompanied by sufficient photographic documentation, and only in occasional cases could one raise some doubts about the cytodiagnostic interpretation provided by the authors.

A limitation is the lack of homogeneity and standardisation in the laboratory methods used to prepare the PB film. Virtually no article describes in an exhaustive way the protocols adopted, with particular reference to the time elapsed between sampling, storage of the blood in an ethylenediamine tetra-acetic acid (EDTA) anticoagulated tube, spreading of a film of anticoagulated blood (or possibly immediate execution of the film without anticoagulation), fixation and staining. Using different models of automated film makers and stainers for microscope review and application of coverslips can be another methodological variable worth mentioning in manuscripts describing cell morphology.

Storage-induced cytological lesions can sometimes overlap with COVID-19-related leucocyte aberrations[106]: neutrophils and, less frequently, lymphocytes can undergo apoptosis in the EDTA tube with loss of chromatin structure, monocyte vacuolisation tends to increase with time, lymphocyte fragility in lymphoproliferative disorders can increase during storage. Such changes are time and temperature dependent.[107] There is almost no information concerning the time and temperature between blood collection and film preparation in the literature we evaluated. The 'Materials and Methods' sections, in future works, should include a detailed description of such methodological variables to avoid false increases, development or disappearance of nuclear and cytoplasmic anomalies.

The heterogeneity of morphological descriptions in the different papers represents a source of possible confusion for readers and future researchers. Standardisation committees and expert groups have recently published guidelines that include efforts toward standardisation of nomenclature and terminology in morphology and cell counting in haematology, which could be of help in harmonising cell anomalies' descriptions.[66,67] In particular, digital cell analysers should be considered, especially as far as their increased capacity to count smudge cells and their still unknown accuracy in flagging neutrophil and monocyte abnormalities in COVID-19 are concerned.[11,16,18,35,37,40,42,49,50]

From a diagnostic standpoint, studies on the absolute enumeration of neutrophils and, even more importantly, eosinophils generally lack an accurate record of patients'

treatment, underscoring the possible effects of administration of corticosteroids, which can accentuate eosinopenia and promote neutrophilia, and possible effects of other medications.

Finally, almost all studies have been conducted on hospitalised patients. Therefore, data on blood cell abnormalities in the great majority of patients with mild COVID-19 or with asymptomatic SARS-CoV-2 infection are not yet available.

## DISCUSSION

Quantitative and qualitative blood cell features in hospitalised patients with COVID-19 provide plenty of information. Due to diverging changes in their absolute count, the neutrophil-to-lymphocyte ratio has a well-established diagnostic and prognostic value. Morphological aberrations of such cells in the PB film are plentiful, and the scientific literature, although not homogeneous in article type and quality, allows us to delineate a typical blood cell profile in hospitalised patients with COVID-19, with clinical and physiopathological correlates (Figure 4).

Morphological alterations of lymphocytes are universally present in COVID-19. They are heterogeneous and cover the full spectrum of morphological abnormalities seen in infectious diseases associated with important reactive lymphocytosis, such as infectious mononucleosis, with large cells with light blue cytoplasm and immature-looking, lymphoplasmacytoid cells, and an increased proportion of LGLs (in contrast with the immunophenotypic data of decreased $CD16^{+}$, $CD56^{+}$ cells). In general terms, lymphocyte morphological changes in COVID-19 can be considered intense but not specific and not dissimilar from those observed in other viral infections. Lymphocytes of atypical shapes are heterogeneous and variably combined. Although frequently significant even in lymphocytopenic patients, they are not individually specific for COVID-19 and tend to repeat the aspects of reactive lymphocytosis that we observe, e.g., in EBV, CMV or parvovirus infections. The prognostic value of lymphocyte morphology in COVID-19 has been variously related to a better or a worse prognosis and remains uncertain. The appearance and numerical increase in large or plasmacytoid lymphocytes is a relatively late phenomenon[49] and, in our early experience, often heralded clinical recovery in severely ill patients,[39] having an opposite significance to worsening lymphocytopenia. COVID-19 monocytes often display a homogeneous, moderately atypical aspect, consisting of large size and extensively vacuolated cytoplasm. Such morphology correlates with a state of cellular activation and the expression of pro-inflammatory markers, such as IL-8 and IL-6.[14,38,75,108] The prognostic significance of such extensive monocyte vacuolisation is uncertain.

Neutrophilia, on the other hand, is prognostically unfavourable. The neutrophil-to-lymphocyte ratio is currently accepted as a helpful indicator of disease evolution, and high values are associated with an increased risk of death in ICU patients.[73,74] Neutrophil toxic granules are a common finding in infections. In contrast, hypergranular and hypogranular neutrophils' co-existence is more typical of severe COVID-19. Such cytoplasmic features can be correlated with recent studies showing abnormal neutrophil degranulation and, in particular, dysregulation of the release of primary granule enzymes MPO and elastase as a result of direct SARS-CoV-2 infection of human neutrophils.[109] MPO and elastase are components of neutrophil extracellular traps (NETs). We recently found, using an automated cytochemical analyser, that frequency of partial MPO deficiency in PB samples from hospitalised COVID-19 cases was increased,[58] possibly indicating granule release related to disease activity. Other automated FBC analysers can measure morphometric parameters or cell population data (CPD) of neutrophils and other cells, which could indicate states of activation or degradation. The first published results indicate that, although CPD largely depends on the technology used,[110,111] increased monocyte volume heterogeneity,[76,77] and less granular and smaller neutrophils are among the most interesting findings.[11]

According to the majority of the articles we have analysed, among the many atypical findings in PB films of patients with at least moderate or severe COVID-19, nuclear hyposegmentation is the most distinctive morphological feature of COVID-19 neutrophils. Disturbed nuclear segmentation, associated with the PPH anomaly with a peculiar

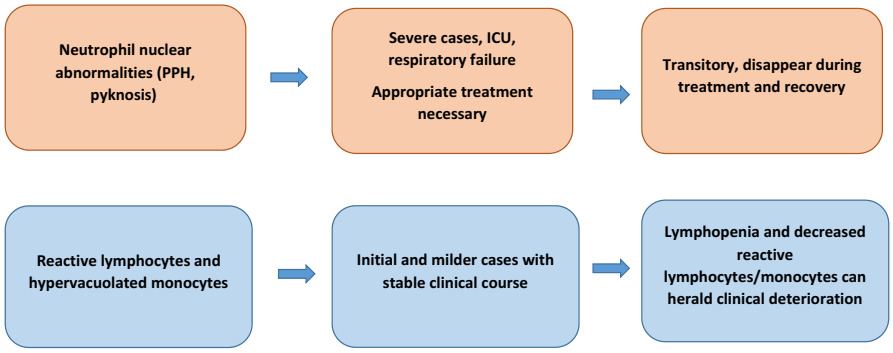


**FIGURE 4** Clinical correlations of morphological findings in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. ICU, intensive care unit; PPH, pseudo-Pelger-Huët.

hypercondensation of nuclear chromatin, proceeding from abnormal clumping to complete loss of structure in dark masses to colliquation and apoptosis, is the dominant morphological expression that the majority of authors have highlighted in their description. The nuclear profile varies from a small, rounded mass to a bilobed, often asymmetrical, pince-nez shape, to a band or rod-like contour. These changes, when present in a significant proportion (i.e., >10% of neutrophils) are found in patients with severe disease, often progressing to respiratory failure (followed or not by recovery) and have a prognostic unfavourable value.[42]

The PPH morphology is usually related to haematological disorders with myelodysplasia, infectious and immune diseases, and use of several drugs.[112,113] The peculiar type of PPH anomaly observed in severe COVID-19 displays an apparent evolution toward apoptosis and lends itself, based on very recent studies, to far-reaching pathophysiological considerations, which certainly go beyond the boundaries and objectives of this morphological review. It will be sufficient here to recall the links between morphology and the neutrophil hyperactive state described in the severe COVID-19 cytokine storm. The PPH anomaly and other abnormalities of neutrophils in COVID-19 are likely the morphological expressions of the multiple abnormalities of neutrophil function and maturation, which these cells display when they are studied with classical or innovative technological methods. Neutrophils in COVID-19 show an immature phenotype and many dysfunctional features.[114] The study of circulating neutrophils in COVID-19 with modern techniques of transcriptomics and RNA-sequencing, flow and mass cytometry, and metabolic and functional analysis have shown heterogeneity and immaturity features with signs of recent activation, enhanced capacity for NET formation, immunosuppressive capacity against T-cell proliferation and lower density due to reduced granulation.[115] Compromised oxygen exchange in severe COVID-19 cases likely depends on developing a cytokine storm, which devolves into NET formation in pulmonary spaces and microvessels.[15,116] Nuclear changes in COVID-19 films display possible similarities to those experimentally described in NET formation or NETosis.[117] When a stimulated neutrophil undergoes NETosis, the multilobular nucleus tends to modify its profile, lose the lobular shape, and round up. NETs are released via cell lysis (possibly related to the reported abundance of smudge cells). In other cases, the nuclear membrane can remain intact with the release of some nuclear vesicles containing DNA, after which chromatin condensation and loss of structure occur (apoptotic nuclei).[117] Nuclear morphology of the acquired and transitory PPH anomaly (round nuclei with hypercondensed chromatin) is evocative of nuclear changes observed during NETosis: profile rounding, bleb formation, chromatin decondensation and condensation, nuclear rupture, and disassembly. Interestingly, increased expression of the scaffolding proteins, lamins, in the neutrophil nuclear membrane, which controls nuclear membrane shape, is combined with nuclear rounding in activated neutrophils.[117] Moreover, the rare hereditary Pelger-Huët anomaly is characterised by hypolobulated or rounded neutrophil nuclei due to an autosomal mutation of lamin B receptor (*LBR* gene),[118] and studies on the PPH anomaly seen in neutrophils of a mouse model with systemic lupus erythematosus (SLE) have shown aberrant mis-splicing of the *LBR* transcript.[119] The link of the typical changes in nuclear shape in NETosis, hereditary Pelger-Huët anomaly, SLE and medication-related PPH with COVID-19 PPH is evocative of a common physiopathological mechanism possibly involving anomalies of the LBR protein function, NET release and neutrophil activation.[117]

Neutrophils have a role in the pathogenesis of thrombosis in COVID-19.[120] Platelet activation, morphologically visible as giant forms, granule increase or decrease, and presence of cytoplasmic protrusions and pseudopods, appears as an almost universal finding in films obtained from hospitalised patients with COVID-19. The activated platelet state can have a link with neutrophil activation and can correspond to the described neutrophil–platelet interactions leading to the so-called immunothrombosis in the microvasculature, where mixed platelet–neutrophil thrombi have been described.[121]

Finally, the report of TTP with increased schistocytes in the PB film as a sign of COVID-19 or TTP development in patients with COVID-19, suggests a possible association between the two conditions. SARS-CoV-2 has thus to be included among the different RNA viruses associated with TTP, first of all HIV, for which a pathogenetic role has been proposed or demonstrated.[122]

From a cytomorphological differential diagnosis standpoint, the COVID-19 PB film changes should not be confused with primary haematological disorders. Chronic myelomonocytic leukaemia can be excluded by the rarity of increased monocyte count, the specific type of cytoplasmic vacuolation and the absence of immature monocytes and monoblasts in COVID-19. In some cases, marked neutrophil dysmorphism combined with a leucoerythroblastic picture can have analogies with myelodysplastic syndromes or, even, idiopathic myelofibrosis. Based on the awareness of the specific COVID-19 morphological features, the clinical context and the transitory nature of the anomalies, any possible confusion can easily be avoided.

In conclusion, morphological anomalies of blood cells in COVID-19 likely have physiopathological bases to be understood, and some have substantial prognostic significance. From a haematology laboratory standpoint, it is clear from the collected data that an expert morphologist is fundamental in their recognition and description. This work cannot be delegated entirely to the currently available digital morphology analysers. The experience with COVID-19 PB films reminds us that we cannot yet do without a microscope on the laboratory bench and, above all, without expert and attentive operators who do not miss on the slide or on the screen of a digital analyser, subtle variations in shape or colour of cellular structures capable of opening the way to new paths to knowledge.

## AUTHOR CONTRIBUTIONS

Gina Zini and Giuseppe d'Onofrio reviewed the literature, analysed the data, and wrote the paper.

## ACKNOWLEDGEMENT

Open Access Funding provided by Universita Cattolica del Sacro Cuore within the CRUI-CARE Agreement.

## CONFLICT OF INTEREST

The authors have no conflict of interests.

## DATA AVAILABILITY STATEMENT

Data is available on request.

## ORCID

*Gina Zini* https://orcid.org/0000-0003-0782-294X
*Giuseppe d'Onofrio* https://orcid.org/0000-0003-1948-3092

## REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China Lancet. 2020;395:497–506.
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou C, He J, et al. China medical treatment expert group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.
3. Zhang H, Cao X, Kong M, Mao X, Huang L, He P, et al. Clinical and hematological characteristics of 88 patients with COVID-19. Int J Lab Hematol. 2020;42:780–7.
4. Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. Int J Lab Hematol. 2020;42(Suppl 1):11–8.
5. Erdinc B, Sahni S, Gotlieb V. Hematological manifestations and complications of COVID-19. Adv Clin Exp Med. 2021;30:101–7.
6. Wang C, Deng R, Gou L, Fu Z, Zhang X, Shao F, et al. Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. Ann Transl Med. 2020;8:593.
7. Gajendra S. Spectrum of hematological changes in COVID-19. Am J Blood Res. 2022;12:43–53.
8. Pereira-Roche N, Roblejo-Balbuena H, Marín-Padrón LC, Izaguirre-Rodríguez R, Sotmomayor-Lugo F, Zúñiga-Rosales Y, et al. Hematological alterations in patients recovered from SARS-CoV-2 infection in Havana. Cuba MEDICC Rev. 2022;24:7–14.
9. Elshazli RM, Toraih EA, Elgaml A, El-Mowafy M, El-Mesery M, Amin MN, et al. Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: a meta-analysis of 6320 patients. PLoS One. 2020;15:e0238160.
10. Khartabil TA, Russcher H, van der Ven A, de Rijke YB. A summary of the diagnostic and prognostic value of hemocytometry markers in COVID-19 patients. Crit Rev Clin Lab Sci. 2020;57:415–31.
11. 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. 2021;155:364–75.
12. Bell R, Zini G, d'Onofrio G, Rogers HJ, Lee YS, Frater JL. The hematology laboratory's response to the COVID-19 pandemic: a scoping review. Int J Lab Hematol. 2021;43:148–59.
13. Chan SSW, Christopher D, Tan GB, Chong VCL, Fan BE, Lin CY, et al. Peripheral lymphocyte subset alterations in COVID-19 patients. Int J Lab Hematol. 2020;42:e199–e203.
14. Lagadinou M, Zareifopoulos N, Gkentzi D, Sampsonas F, Kostopoulou E, Marangos M, et al. Alterations in lymphocyte subsets and monocytes in patients diagnosed with SARS-CoV-2 pneumonia: a mini review of the literature. Eur Rev Med Pharmacol Sci. 2021;25:5057–62.
15. Mehta P, Fajgenbaum DC. Is severe COVID-19 a cytokine storm syndrome: a hyperinflammatory debate. Curr Opin Rheumatol. 2021;33:419–30.
16. Chong VCL, Lim KGE, Fan BE, Chan SSW, Ong KH, Kuperan P. Reactive lymphocytes in patients with COVID-19. Br J Haematol. 2020;189:844.
17. Foldes D, Hinton R, Arami S, Bain BJ. Plasmacytoid lymphocytes in SARS-CoV-2 infection (Covid-19). Am J Hematol. 2020;95:861–2.
18. Jerez J, Ernst DM. High percentage of smudge cells in a patient with COVID19: rediscovering their utility. EJHaem. 2020;1:374–5.
19. Lee CT, Teo WZY. Peripheral blood smear demonstration of lymphocyte changes in severe COVID-19. Am J Trop Med Hyg. 2020;103:1350–1.
20. Lanza L, Koroveshi B, Barducchi F, Lorenzo A, Venturino E, Cappelli E, et al. A new diagnosis of monoclonal B-cell lymphocytosis with cytoplasmic inclusions in a patient with COVID-19. Am J Hematol. 2022;97:1372–3. https://doi.org/10.1002/ajh.26582
21. Singh A, Sood N, Narang V, Goyal A. Morphology of COVID-19-affected cells in peripheral blood film. BMJ Case Rep. 2020;13:e236117.
22. Akçabelen YM, Gürlek Gökçebay D, Yaralı N. Dysplastic changes of peripheral blood cells in COVID-19 infection. Turk J Haematol. 2021;38:72–3.
23. Ahnach M, Ousti F. Blood cells morphology change with COVID-19. Pan Afr Med J. 2020;35(Suppl 2):45.
24. Cantu MD, Towne WS, Emmons FN, Mostyka M, Borczuk A, Salvatore SP, et al. Clinical significance of blue-green neutrophil and monocyte cytoplasmic inclusions in SARS-CoV-2 positive critically ill patients. Br J Haematol. 2020;190:e89–e92.
25. Gérard D, Henry S, Thomas B. SARS-CoV-2: a new aetiology for atypical lymphocytes. Br J Haematol. 2020;189:845.
26. Salib C, Teruya-Feldstein J. Hypersegmented granulocytes and COVID-19 infection. Blood. 2020;135:2196.
27. Lee WS, Margolskee E. Leukoerythroblastosis and plasmacytoid lymphocytes in a child with SARS-CoV-2-associated multisystem inflammatory syndrome. Blood. 2020;136:914.
28. Mitra A, Dwyre DM, Schivo M, Thompson GR 3rd, Cohen SH, Ku N, et al. Leukoerythroblastic reaction in a patient with COVID-19 infection. Am J Hematol. 2020;95:999–1000.
29. Jones JR, Ireland R. Morphological changes in a case of SARS-CoV-2 infection. Blood. 2020;135:2324.
30. Aladily TN, Alnahhal J, Alshorman A, Awidi A. Transient increase in blast count following COVID-19 infection mimicking acute leukemia. Int J Lab Hem. 2021;43:339–40.
31. El Jamal SM, Salib C, Stock A, Uriarte-Haparnas NI, Glicksberg BS, Teruya-Feldstein J, et al. Atypical lymphocyte morphology in SARS-CoV-2 infection. Pathol Res Pract. 2020;216:153063.
32. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020;95:E131–E134.
33. Liu X, Zhang R, He G. Hematological findings in coronavirus disease 2019: indications of progression of disease. Ann Hematol. 2020;99:1421–8.
34. Osman J, Lambert J, Templé M, Devaux F, Favre R, Flaujac C, et al. Rapid screening of COVID-19 patients using white blood cell scattergrams, a study on 381 patients. Br J Haematol. 2020;190:718–22.
35. Merino A, Vlagea A, Molina A, Egri N, Laguna J, Barrera K, et al. Atypical lymphoid cells circulating in blood (1–15%) in COVID-19 infection: morphology, immunophenotype and prognosis value. J Clin Pathol. 2020;11:207087.
36. Weinberg SE, Behdad A, Ji P. Atypical lymphocytes in peripheral blood of patients with COVID-19. Br J Haematol. 2020;190:36–9.
37. Sugihara J, Shibata S, Doi M, Shimmura T, Inoue S, Matsumoto O, et al. Atypical lymphocytes in the peripheral blood of COVID-19 patients: a prognostic factor for the clinical course of COVID-19. PLoS One. 2021;16:e0259910.
38. Zhang D, Guo R, Lei L, Liu H, Wang Y, Wang Y, et al. COVID-19 infection induces readily detectable morphologic and inflammation-related phenotypic changes in peripheral blood monocytes. J Leukoc Biol. 2021;109:13–22.

39. Zini G, Bellesi S, Ramundo F, d'Onofrio G. Morphological anomalies of circulating blood cells in COVID-19. Am J Hematol. 2020;95:870–2.
40. Sadigh S, Massoth L, Christensen B, Stefely J, Keefe J, Sohani A. Peripheral blood morphologic findings in patients with COVID-19. Int J Lab Hematol. 2020;42:e248–51.
41. Lüke F, Orsó E, Kirsten J, Poeck H, Grube M, Wolff D, et al. Coronavirus disease 2019 induces multi-lineage, morphologic changes in peripheral blood cells. EJHaem. 2020;1:376–83.
42. Nazarullah A, Liang C, Villarreal A, Higgins RA, Mais DD. Peripheral blood examination findings in SARS-CoV-2 infection. Am J Clin Pathol. 2020;154:319–29.
43. Singh S, Madan J, Nath D, Tiwari N. Peripheral blood smear morphology- a red flag in COVID-19. Int J Trop Dis Health. 2020;2020(41):54–8.
44. Schapkaitz E, De Jager T, Levy B. The characteristic peripheral blood morphological features of hospitalized patients infected with COVID-19. Int J Lab Hematol. 2021;43(3):e130–34.
45. 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;3:95–108.
46. Ahnach M, Ousti F, Nejjari S, Houssaini MS, Dini N. Peripheral blood smear findings in COVID-19. Turk J Haematol. 2020;37:310–2.
47. Berber I, Cagasar O, Sarici A, Berber NK, Aydogdu I, Ulutas O, et al. Peripheral blood smear findings of COVID-19 patients provide İnformation about the severity of the disease and the duration of hospital stay. Mediterr J Hematol Infect Dis. 2021;13:e2021009.
48. Gabr H, Bastawy S, Abdel Aal AA, Khalil NM, Fateen M. Changes in peripheral blood cellular morphology as diagnostic markers for COVID-19 infection. Int J Lab Hematol. 2022;44:454–60.
49. Horiuchi Y, Hayashi F, Iwasaki Y, Matsuzaki A, Nishibe K, Kaniyu K, et al. Peripheral granular lymphocytopenia and dysmorphic leukocytosis as simple prognostic markers in COVID-19. Int J Lab Hematol. 2021;43:1309–18.
50. Alnor A, Sandberg MB, Toftanes BE, Vinholt PJ. Platelet parameters and leukocyte morphology is altered in COVID-19 patients compared to non-COVID-19 patients with similar symptomatology. Scand J Clin Lab Invest. 2021;81:213–7.
51. Kaur G, Sandeep F, Olayinka O, Gupta G. Morphologic changes in circulating blood cells of COVID-19 patients. Cureus. 2021;13:e13416.
52. Pezeshki A, Vaezi A, Nematollahi P. Blood cell morphology and COVID-19 clinical course, severity, and outcome. J Hematop. 2021;14:221–8.
53. Refaat L, Abdellateif MS, Bayoumi A, Khafagy M, Kandeel EZ, Nooh HA. Detection of abnormal lymphocytes in the peripheral blood of COVID-19 cancer patients: diagnostic and prognostic possibility. Hematology. 2022;27:745–56.
54. Jain S, Meena R, Kumar V, Kaur R, Tiwari U. Comparison of hematologic abnormalities between hospitalized coronavirus disease 2019 positive and negative patients with correlation to disease severity and outcome. J Med Virol. 2022;94:3757–67.
55. Singh A, Verma SP, Kushwaha R, Ali W, Reddy HD, Singh US. Hematological changes in the second wave of SARS-CoV-2 in North India. Cureus. 2022;14:e23495.
56. Zini G, Arcuri P, Ladiana R, Tanzarella ES, De Pascale G, d'Onofrio G. Vaccination does not affect leukocyte morphologic abnormalities of severe COVID-19. Am J Hematol. 2022;97(8):E310–11.
57. Kosmeri C, Koumpis E, Tsabouri S, Siomou E, Makis A. Hematological manifestations of SARS-CoV-2 in children. Pediatr Blood Cancer. 2020;67:e28745.
58. Rahman A, Niloofa R, Jayarajah U, De Mel S, Abeysuriya V, Seneviratne SL. Hematological abnormalities in COVID-19: a narrative review. Am J Trop Med Hyg. 2021;104:1188–201.
59. Wiggill TM, Mayne ES, Vaughan JL, Louw S. Overview of the Haematological effects of COVID-19 infection. Adv Exp Med Biol. 2021;1321:163–72.
60. Karimi Shahri M, 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;43:160–8.
61. Rosenberg HF, Foster PS. Eosinophils and COVID-19: diagnosis, prognosis, and vaccination strategies. Semin Immunopathol. 2021;43:383–92.
62. Murphy P, Glavey S, Quinn J. Anemia and red blood cell abnormalities in COVID-19. Leuk Lymphoma. 2021;62:1539.
63. Saluja P, Gautam N, Yadala S, Venkata AN. Thrombotic thrombocytopenic purpura (TTP) after COVID-19 vaccination: a systematic review of reported cases. Thromb Res. 2022;214:115–21.
64. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis. 2020;221:1762–9.
65. Huang W, Berube J, McNamara M, Saksena S, Hartman M, Arshad T, et al. Lymphocyte subset counts in COVID-19 patients: a meta-analysis. Cytometry A. 2020;97:772–6.
66. Palmer L, Briggs C, McFadden S, Zini G, Burthem J, Rozenberg G, et al. ICSH recommendations for the standardization of nomenclature and grading of peripheral blood cell morphological features. Int J Lab Hematol. 2015;37:287–303.
67. Zini G, Bain B, Bettelheim P, Cortez J, d'Onofrio G, Faber E, et al. A European consensus report on blood cell identification: terminology utilized and morphological diagnosis concordance among 28 experts from 17 countries within the European LeukemiaNet network WP10, on behalf of the ELN morphology faculty. Br J Haematol. 2010;151:359–64.
68. Rastogi N. COVID-19 lymphocyte morphology – a very sensitive parameter in diagnosing COVID-19 from peripheral blood smear. Asian Pac J Health Sci. 2020;7:42–4.
69. Berg RMG, Ronit A, Rørvig SB, Plovsing RR. Atypical lymphocytes in bronchoalveolar lavage fluid from patients with COVID-19 ARDS. Pathol Res Pract. 2020;216:153242.
70. Merino A, Laguna J, Molina A, Vlagea A, Sibila O. SARS-CoV-2 pneumonia and atypical lymphocyte morphology in pleural fluid. Int J Lab Hematol. 2022;44:e1–e3.
71. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46:846–8.
72. Shi L, Wang Y, Liang X, Xiao W, Duan G, Yang H, et al. Is neutrophilia associated with mortality in COVID-19 patients? A meta-analysis and meta-regression. Int J Lab Hematol. 2020;42:e244–47.
73. La Torre G, Marte M, Massetti AP, Carli SM, Romano F, Mastroianni CM, et al. COVID-collaborative group. The neutrophil/lymphocyte ratio as a prognostic factor in COVID-19 patients: a case-control study. Eur Rev Med Pharmacol Sci. 2022;26:1056–64.
74. Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: a retrospective cross-sectional study. J Med Virol. 2020;92:2573–81.
75. Alzaid F, Julla JB, Diedisheim M, Potier C, Potier L, Velho G, et al. Monocytopenia, monocyte morphological anomalies and hyperinflammation characterise severe COVID-19 in type 2 diabetes. EMBO Mol Med. 2020;12:e13038.
76. Ognibene A, Lorubbio M, Magliocca P, Tripodo E, Vaggelli G, Iannelli G, et al. Elevated monocyte distribution width in COVID-19 patients: the contribution of the novel sepsis indicator. Clin Chim Acta. 2020;509:22–4.
77. Zeng X, Xing H, Wei Y, Tang Z, Lu X, Wang Z, et al. Monocyte volumetric parameters and lymph index are increased in SARS-CoV-2 infection. Int J Lab Hematol. 2020;42:e266–69.
78. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75:1730–41.
79. Soni M. Evaluation of eosinopenia as a diagnostic and prognostic indicator in COVID-19 infection. Int J Lab Hematol. 2021;43(Suppl 1):137–41.
80. Nair AP, Soliman A, Al Masalamani MA, De Sanctis V, Nashwan AJ, Sasi S, et al. Clinical outcome of eosinophilia in patients with COVID-19: a controlled study. Acta Biomed. 2020;91:e2020165.

81. Chen J, Pan Y, Li G, Xu W, Zhang L, Yuan S, et al. Distinguishing between COVID-19 and influenza during the early stages by measurement of peripheral blood parameters. J Med Virol. 2021;93:1029–37.
82. Buoro S, Di Marco F, Rizzi M, Fabretti F, Lorini FL, Cesa S, et al. Papa Giovanni XXIII Bergamo hospital at the time of the COVID-19 outbreak: letter from the warfront…. Int J Lab Hematol. 2020;42(Suppl 1):8–10. https://doi.org/10.1111/ijlh.13207
83. Bellmann-Weiler R, Lanser L, Barket R, Rangger L, Schapfl A, Schaber M, et al. Prevalence and predictive value of anemia and dysregulated iron homeostasis in patients with COVID-19 infection. J Clin Med. 2020;9:2429.
84. Foy BH, Carlson JCT, Reinertsen E, Valls PI, Pallares Lopez R, et al. Association of red blood cell distribution width with mortality risk in hospitalized adults with SARS-CoV-2 infection. JAMA Netw Open. 2020;3:e2022058.
85. Lee JJ, Montazerin SM, Jamil A, Jamil U, Marszalek J, Chuang ML, et al. Association between red blood cell distribution width and mortality and severity among patients with COVID-19: a systematic review and meta-analysis. J Med Virol. 2021;93:2513–22.
86. Ramachandran P, Gajendran M, Perisetti A, Elkholy KO, Chakraborti A, Lippi G, et al. Red blood cell distribution width in hospitalized COVID-19 patients. Front Med. 2022;8:582403.
87. Berzuini A, Bianco C, Migliorini AC, Maggioni M, Valenti L, Prati D. Red blood cell morphology in patients with COVID-19-related anaemia. Blood Transfus. 2021;19:34–6.
88. Altowyan E, Alnujeidi O, Alhujilan A, Alkathlan M. COVID-19 presenting as thrombotic thrombocytopenic purpura (TTP). BMJ Case Rep. 2020;13:12.
89. Beaulieu MC, Mettelus DS, Rioux-Massé B, Mahone M. Thrombotic thrombocytopenic purpura as the initial presentation of COVID-19. J Thromb Haemost. 2021;19:1132–4.
90. Darnahal M, Azhdari Tehrani H, Vaezi M, Haghighi S. Covid-19 and thrombotic thrombocytopenic purpura: a case report. Int J Hematol Oncol Stem Cell Res. 2021;15:72–4.
91. Al-Ansari RY, Bakkar M, Abdalla L, Sewify K. Critical care COVID-19 patient with a picture of thrombotic thrombocytopenic purpura. Eur J Case Rep Intern Med. 2020;7:002143.
92. Tehrani HA, Darnahal M, Vaezi M, Haghighi S. COVID-19 associated thrombotic thrombocytopenic purpura (TTP); a case series and mini-review. Int Immunopharmacol. 2021;93:107397.
93. Crossette-Thambiah C, Hazarika B, Bain BJ. COVID-19 and acute kidney injury. Am J Hematol. 2021;96:747–8.
94. Zini G, d'Onofrio G, Erber WN, Lee SH, Nagai Y, Basak GW, et al. 2021 update of the 2012 ICSH recommendations for identification, diagnostic value, and quantitation of schistocytes: impact and revisions. Int J Lab Hematol. 2021;43:1264–71.
95. Della Rocca DG, Magnocavallo M, Lavalle C, Romero J, Forleo GB, Tarantino N, et al. Evidence of systemic endothelial injury and microthrombosis in hospitalized COVID-19 patients at different stages of the disease. J Thromb Thrombolysis. 2021;51:571–6.
96. Martinelli N, Montagnana M, Pizzolo F, Friso S, Salvagno GL, Forni GL, et al. A relative ADAMTS13 deficiency supports the presence of a secondary microangiopathy in COVID 19. Thromb Res. 2020;193:170–2.
97. Deucher W, Sukumar S, Cataland SR. Clinical relapse of immune-mediated thrombotic thrombocytopenic purpura following COVID-19 vaccination. Res Pract Thromb Haemost. 2022;6:e12658.
98. Hammami E, Lamarque M, Aujoulat O, Debliquis A, Drénou B, Harzallah I. Acquired thrombotic thrombocytopenic purpura after BNT162b2 COVID-19 vaccine: case report and literature review. Lab Med. 2022;28:lmac016.
99. Maayan H, Kirgner I, Gutwein O, Herzog-Tzarfati K, Rahimi-Levene N, Koren-Michowitz M, et al. Acquired thrombotic thrombocytopenic purpura: a rare disease associated with BNT162b2 vaccine. J Thromb Haemost. 2021;19:2314–7.
100. Osmanodja B, Schreiber A, Schrezenmeier E, Seelow E. First diagnosis of thrombotic thrombocytopenic purpura after SARS-CoV-2 vaccine - case report. BMC Nephrol. 2021;22:411.
101. Laverdure E, Sperlich C, Fox S. Refractory immune TTP following Pfizer-BioNTech COVID-19 vaccine successfully salvaged with caplacizumab. J Thromb Haemost. 2022;20:1696–8.
102. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta. 2020;506:145–8.
103. Rohlfing AK, Rath D, Geisler T, Gawaz M. Platelets and COVID-19. Hamostaseologie. 2021;41:379–5.
104. Comer SP, Cullivan S, Szklanna PB, Weiss L, Cullen S, Kelliher S, et al. COCOON study investigators. COVID-19 induces a hyperactive phenotype in circulating platelets. PLoS Biol. 2021;19:e3001109.
105. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, Teixeira L, Barreto EA, Pão CRR, et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood. 2020;136:1330–41.
106. Vives-Corrons JL, Briggs C, Simon-Lopez R, Albarede S, de la Salle B, Flegar-Meatrii Z, et al. Effect of EDTA-anticoagulated whole blood storage on cell morphology examination. A need for standardization. Int J Lab Hematol. 2014;36:222–6.
107. Zini G, International Council for Standardization in Haematology (ICSH). Stability of complete blood count parameters with storage: toward defined specifications for different diagnostic applications. Int J Lab Hematol. 2014;36:111–3.
108. Knoll R, Schultze JL, Schulte-Schrepping J. Monocytes and macrophages in COVID-19. Front Immunol. 2021;12:720109.
109. Muralidharan A, Wyatt TA, Reid SP. SARS-CoV-2 dysregulates neutrophil degranulation and reduces lymphocyte counts. Biomedicine. 2022;10:382–93.
110. Vasse M, Ballester MC, Ayaka D, Sukhachev D, Delcominette F, Habarou F, et al. Interest of the cellular population data analysis as an aid in the early diagnosis of SARS-CoV-2 infection. Int J Lab Hematol. 2021;43:116–22.
111. Naoum FA, Ruiz ALZ, Martin FHO, Brito THG, Hassem V, Oliveira MGL. Diagnostic and prognostic utility of WBC counts and cell population data in patients with COVID-19. Int J Lab Hematol. 2021;43(Suppl 1):124–8.
112. Dusse LM, Moreira AM, Vieira LM, Rios DR, Silva RM, Carvalho M. Acquired Pelger-Huët: what does it really mean? Clin Chim Acta. 2010;411:1587–90.
113. Wang E, Boswell E, Siddiqi I, Lu CM, Sebastian S, Rehder C, et al. Pseudo-Pelger-Huët anomaly induced by medications: a clinicopathologic study in comparison with myelodysplastic syndrome-related pseudo-Pelger-Huët anomaly. Am J Clin Pathol. 2011;135:291–303.
114. Cavalcante-Silva LHA, Carvalho DCM, Lima ÉA, Galvão JGFM, da Silva JSF, Sales-Neto JM, et al. Neutrophils and COVID-19: the road so far. Int Immunopharmacol. 2021;90:107233.
115. Reusch N, De Domenico E, Bonaguro L, Schulte-Schrepping J, Baßler K, Schultze JL, et al. Neutrophils in COVID-19. Front Immunol. 2021;12:652470.
116. Ng H, Havervall S, Rosell A, Aguilera K, Parv K, von Meijenfeldt FA, et al. Circulating markers of neutrophil extracellular traps are of prognostic value in patients with COVID-19. Arterioscler Thromb Vasc Biol. 2021;41:988–94.
117. Manley HR, Keightley MC, Lieschke GJ. The neutrophil nucleus: an important influence on neutrophil migration and function. Front Immunol. 2018;9:2867.
118. Hoffmann K, Dreger CK, Olins AL, Olins DE, Shultz LD, Lucke B, et al. Mutations in the gene encoding the Lamin B receptor produce an altered nuclear morphology in granulocytes (Pelger-Huet anomaly). Nat Genet. 2002;31:410–4.
119. Singh N, Johnstone DB, Martin KA, Tempera I, Kaplan MJ, Denny MF. Alterations in nuclear structure promote lupus autoimmunity in a mouse model. Dis Model Mech. 2016;9:885–97.

120. Iliadi V, Konstantinidou I, Aftzoglou K, Iliadis S, Konstantinidis TG, Tsigalou C. The emerging role of neutrophils in the pathogenesis of thrombosis in COVID-19. Int J Mol Sci. 2021;22:5368.
121. Iba T, Levy JH. The roles of platelets in COVID-19-associated coagulopathy and vaccine-induced immune thrombotic thrombocytopenia. Trends Cardiovasc Med. 2022;32:1–9.
122. Lopes da Silva R. Viral-associated thrombotic microangiopathies. Hematol/Oncol Stem Cell Ther. 2011;4:51–9.

**How to cite this article:** Zini G, d'Onofrio G. Coronavirus disease 2019 (COVID-19): Focus on peripheral blood cell morphology Br J Haematol. 2022;00:1–16. https://doi.org/10.1111/bjh.18489