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REVIEW ARTICLE

Hematological findings in coronavirus disease 2019: indications of progression of disease

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Abstract

Coronavirus disease 2019 (COVID-19) is a new human infectious disease. The etiology for this outbreak is a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Thus far, related research on COVID-19 is still in preliminary stage. This paper summarized the latest outcomes of corresponding study from Chinese centers and clarified the hematopoietic abnormality caused by SARS-CoV-2 and potential mechanism. Lymphopenia was common in the early stage after the onset of COVID-19. A significant decrease was observed in peripheral CD4+ and CD8+ T lymphocytes. As the illness progressed, neutrophilia emerged in several cases, and patients with severe critical pulmonary conditions showed higher neutrophils than common type. Thrombocytopenia was resulting from the consumption and/or the reduced production of platelets in damaged lungs. Anemia was not observed notably, but the decrease in hemoglobin was frequent. The activation of monocyte-macrophage system aggravates the immune damage of lung and other tissues, which leads to the increase of D-dimer, prothrombin time, and platelet consumption.

Keywords SARS-CoV-2 · COVID-19 · Lymphopenia · Neutrophilia · Thrombocytopenia · Hemoglobin

Introduction

Since December 2019, an increasing number of pneumonia cases of unknown reason emerged in Wuhan, China [1]. Deep-sequencing analysis from nasopharyngeal swabs, sputum, lower respiratory tract samples, and blood indicated a novel coronavirus, known as 2019-nCoV [2]. Coronavirus can cause multiple system infections and mainly respiratory infections in human, such as severe acute respiratory syndrome and Middle East respiratory syndrome [3–5]. The novel virus was named 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by WHO; due to more than 79% homology with SARS-CoV, SARS-CoV-2 was responsible for coronavirus disease 2019 (COVID-19) [2]. At presentation, the number of cases increased rapidly, but related information regarding the clinical features and hematological changes of infected patients is limited [4–7].

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Initially reported clinical characteristics of COVID-19 mainly focused on inpatients, while a few SARS-CoV-2 infections may be with no or mild pneumonia-related symptoms, which belonged to the simple infection type in WHO classification [5–7]. Summarized COVID-19 cases including Hubei and other regions in China, common symptoms were consistent with the non-specific symptoms of acute respiratory infection [3–7]. Reported studies indicated the onset of inflammatory cytokine storms in COVID-19 leaded to progress to severe lung injury, respiratory distress, and multiple organ failure. Through literature analysis (most data from Chinese centers), we found that COVID-19 was prone to cause hematological changes (Table 1). Differences in hematological manifestations were detected between severe and non-severe patients. The severity of COVID-19 is defined according to the clinical management of severe acute respiratory infection when COVID-19 disease is suspected by WHO (version1.2) [2]. Severe illness is designated when the patients have fever or suspected respiratory infection, plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or pulse oximeter oxygen saturation ≤ 93% on room air [2]. Critical illness is defined as patients with acute respiratory distress syndrome or sepsis with acute organ dysfunction [2]. Non-severe type represents patients with the exception

Table 1 Comparisons of demographic and hematologic features between severe and non-severe COVID-19 patients

Variables	References (case number)	Reference value	All patients	Disease severity		
				Non-severe patients	Severe patients	*p* value
Demographic characteristics						
Age, median (IQR/range) or mean (SD), years						
	3 (62)	NA	41 (32–52)	NA	NA	NA
	4 (1099)	NA	47.0 (35.0–58.0)	45.0 (34.0–57.0)	52.0 (40.0–65.0)	< 0.001
	5 (41)	NA	49.0 (41.0–58.0)	49.0 (41.0–57.5)	49.0 (41.0–61.0)	0.60
	6 (99)	NA	55.5 (21–82)	NA	NA	NA
	7 (138)	NA	56 (42–68)	51 (37–62)	66 (57–78)	< 0.001
	11 (201)	NA	51 (43–60)	48.0 (40.0–54.0)	58.5 (50.0–69.0)	< 0.001
	15 (33)	NA	NA	41.8 (22–76)	50(29–68)	0.12
	27 (61)	NA	40 (1–86)	41 (1–76)	56 (34–73)	0.007
	29 (140)	NA	57 (25–87)	51.5 (26–78)	64 (25–87)	< 0.001
	30 (67)	NA	42 (35–54)	41(32–53)	54(47–62)	0.02
Male/female, No.						
	3 (62)	NA	36/27	NA	NA	NA
	4 (1099)	NA	640/459	540/386	100/73	0.967
	5 (41)	NA	30/11	19/9	11/2	0.24
	6 (99)	NA	67/32	NA	NA	NA
	7 (138)	NA	75/63	53/51	22/14	0.34
	11 (201)	NA	128/73	68/49	60/24	0.05
	15 (33)	NA	NA	13/8	9/3	0.46
	27 (61)	NA	31/30	21/23	10/7	0.437
	29 (140)	NA	71/69	38/44	33/25	0.219
	30 (67)	NA	37/30	31/27	6/3	0.72
Blood laboratory findings*						
Lymphocyte count, median (IQR), $\times 10^9$/L						
	3 (62)	0.8–4.0	1.0 (0.8–1.5)	NA	NA	NA
	4 (1099)	NA	1.0 (0.7–1.3)	1.0 (0.8–1.4)	0.8 (0.6–1.0)	< 0.001
	5 (41)	NA	0.8 (0.6–1.1)	1.0 (0.7–1.1)	0.4 (0.2–0.8)	0.0041
	7 (138)	1.1–3.2	0.8 (0.6–1.1)	0.9 (0.6–1.2)	0.8 (0.5–0.9)	0.03
	11 (201)	1.1–3.2	0.91 (0.60–1.29)	1.08 (0.72–1.45)	0.67 (0.49–0.99)	< 0.001
	15 (33)	NA	NA	1.33 (0.28–2.86)	0.86 (0.32–1.69)	0.04
	27 (61)	NA	1.0 (0.8–1.4)	1.1 (0.9–1.4)	0.9 (0.7–1.1)	0.038
	29 (140)	1.1–3.2	0.8 (0.6–1.1)	0.8 (0.6–1.2)	0.7 (0.5–1.0)	0.048
	30 (67)	NA	1.2(0.8–1.6)	1.3 (0.9–1.7)	0.5 (0.48–0.8)	0.0002
Lymphopenia, No./total No. (%)						
	3 (62)	< 1.0	26/62 (42)	NA	NA	NA
	4 (1099)	< 1.5	731/890 (82.1)	584/736 (79.3)	147/154 (95.5)	< 0.001
	5 (41)	< 1.0	26/41 (63)	15/28 (54)	11/13 (85)	0.045
	6 (99)	< 1.1	35/99 (35)	NA	NA	NA
	11 (201)	< 1.1	126/197 (64.0)	NA	NA	NA
	29 (140)	< 1.1	104/138 (75.4)	58/82 (70.7)	46/56 (82.1)	0.160
	30 (67)	NA	24/65 (36.9)	17/56 (30.4)	7/9 (77.8)	< 0.001
CD3, /μL	11 (201)	NA	607.00 (430.50–830.50)	633.00 (467.00–846.00)	446.50 (231.00–633.75)	0.003
CD4, /μL	11 (201)	NA	353.00 (226.50–499.00)	371.00 (283.00–572.00)	234.00 (136.75–398.00)	0.004
CD8, /μL	11 (201)	NA	236.00 (142.50–314.50)	241.00 (159.00–323.00)	157.50 (76.00–289.50)	0.03
Neutrophil count, median (IQR), $\times 10^9$/L						
	3 (62)	2–7	2.9 (2.0–3.7)	NA	NA	NA
	5 (41)	NA	5.0 (3.3–8.9)	4.4 (2.0–6.1)	10.6 (5.0–11.8)	0.00069
	7 (138)	1.8–6.3	3.0 (2.0–4.9)	2.7 (1.9–3.9)	4.6 (2.6–7.9)	< 0.001
	11 (201)	1.8–6.3	4.47 (2.32–7.70)	3.06 (2.03–5.56)	7.04 (3.98–10.12)	< 0.001
	15 (33)	NA	NA	3.36 (1.37–10.03)	4.98 (1.79–12.24)	0.10
	30 (67)	NA	2.6 (2.1–4.1)	2.6 (2.1–3.8)	4.2 (2.1–6.9)	0.17
Neutrophilia, No./total No. (%)						
	6 (99)	> 6.3	38/99 (38)	NA	NA	NA
	11 (201)	> 6.3	68/197 (34.5)	NA	NA	NA

Table 1 (continued)

Variables	References (case number)	Reference value	All patients	Disease severity		
				Non-severe patients	Severe patients	*p* value
NLR	27 (61)	< 3.13	2.6 (1.6–3.5)	2.2 (1.4–3.1)	3.6 (2.5–5.4)	0.003
Leukocytosis, No./total No. (%)						
	5 (41)	> 10	12/40 (30)	5/27 (19)	7/13 (54)	NA
	6 (99)	> 9.5	24/99 (24)	NA	NA	NA
	11 (201)	> 9.5	46/197 (23.4)	NA	NA	NA
	29 (140)	> 9.5	17/138 (12.3)	4/82 (4.9)	13/56 (23.2)	0.003
Platelet count, median (IQR), × 10^9/L						
	3 (62)	83–303	176.0 (135.8–215.5)	NA	NA	NA
	4 (1099)	NA	168.0 (132.0–207.0)	172.0 (139.0–212.0)	137.5 (99.0–179.5)	< 0.001
	5 (41)	NA	164.5 (131.5–263.0)	149.0 (131.0–263.0)	196.0 (165.0–263.0)	0.45
	7 (138)	125–350	163 (123–191)	165 (125–188)	142 (119–202)	0.78
	11 (201)	125–350	180.00 (137.00–241.50)	178.00 (140.00–239.50)	187.00 (124.50–252.50)	0.73
	15 (33)	NA	NA	184.88 (131–292)	194.58 (72–307)	0.64
	27 (61)	NA	164.0 (135.0–219.5)	167.5 (151.0–219.8)	153.0 (120.5–216.0)	0.347
	30 (67)	NA	201 (155–263)	201 (157–263)	217 (154–301)	0.81
Thrombocytopenia, No./total No. (%)						
	3 (62)	< 83	3/62 (5)	NA	NA	NA
	4 (1099)	< 150	315/869 (36.2)	225/713 (31.6)	90/156 (57.7)	< 0.001
	5 (41)	< 100	2/40 (5)	1/27 (4)	1/13 (8)	0.45
	6 (99)	< 125	12/99 (12)	NA	NA	NA
	11 (201)	< 125	37/197 (18.8)	NA	NA	NA
Hemoglobin level, median (IQR) or mean (SD), g/L						
	3 (62)	113–151	137.0 (128.8–152.3)	NA	NA	NA
	4 (1099)	NA	134.0 (119.0–148.0)	135.0 (120.0–148.0)	128.0 (111.8–141.0)	< 0.001
	5 (41)	NA	126.0 (118.0–140.0)	130.5 (120.0–140.0)	122.0 (111.0–128.0)	0.20
	6 (99)	130–175	129.8 (14.8)	NA	NA	NA
	15 (33)	NA	NA	145.24111–162)	125.42 (97–144)	0.002
	27 (61)	NA	138.0 (127.0–150.5)	139.0 (126.5–151.8)	138.0 (127.5–148.0)	0.797
	30 (67)	NA	140(129–152)	142(129–152)	132(125–140)	0.07
D-dimer, median (IQR) or mean (SD), mg/L						
	3 (62)	0–0.7	0.2 (0.2–0.5)	NA	NA	NA
	5 (41)	NA	0.5 (0.3–1.3)	0.5 (0.3–0.8)	2.4 (0.6–14.4)	0.0042
	6 (99)	0–1.5	0.9 (0.5–2.8)	NA	NA	NA
	7 (138)	0–500	203 (121–403)	166 (101–285)	414 (191–1324)	< 0.001
	11 (201)	0–1.5	0.61 (0.35–1.28)	0.52 (0.33–0.93)	1.16 (0.46–5.37)	< 0.001
	15 (33)	NA	NA	0.17 (0.02–0.52)	0.61 (0.08–3.93)	0.09
	29 (140)	0–0.243	0.2 (0.1–0.5)	0.2 (0.1–0.5)	0.4 (0.2–2.4)	< 0.001
D-dimer increased, No./total No. (%)						
	4 (1099)	≥ 0.5	260/560 (46.4)	195/451 (43.2)	65/109 (59.6)	0.003
	6 (99)	> 1.5	36/99 (36)	NA	NA	NA
	11 (201)	> 1.5	44/189 (23.3)	NA	NA	NA
	29 (140)	> 0.243	35/81 (43.2)	12/43 (27.9)	23/38 (60.5)	0.004
Prothrombin time, median (IQR) or mean (SD), s						
	5 (41)	NA	11.1 (10.1–12.4)	10.7 (9.8–12.1)	12.2 (11.2–13.4)	0.012
	6 (99)	10.5–13.5	11.3 (1.9)	NA	NA	NA
	7 (138)	9.4–12.5	13.0 (12.3–13.7)	12.9 (12.3–13.4)	13.2 (12.3–14.5)	0.37
	11 (201)	10.5–13.5	11.10 (10.20–11.90)	10.60 (10.10–11.50)	11.70 (11.10–12.45)	< 0.001
	15 (33)	NA	NA	21.08 (12.1–142)	14.23 (12.7–15.3)	0.46
	27 (61)	NA	12.0 (11.1–13.1)	12.0 (10.8–13.1)	12.0 (11.7–12.6)	0.729

IQR, interquartile range; *SD*, standard deviation; *NA*, not available; *NLR*: neutrophil-to-lymphocyte ratio

*All hematologic abnormalities were determined according to the relevant reference

of the above conditions [2].A blood workup as well as continuous tracking hematological changes could reveal the risks of disease progression.

Hematological findings in COVID-19 patients

Lymphopenia

Lymphopenia generally occurs with leukopenia after coronavirus infection, even white blood cell count remains in normal range. The initial blood count showed moderate lymphopenia ($< 1.0 \times 10^9$/L) in 69.6% cases with SARS, and 33.9% of the patients had leukopenia ($< 3.5 \times 10^9$/L), whereas the neutrophil count and the monocyte count were mostly normal [8]. A study of 157 patients with SARS demonstrated that lymphopenia ($< 1.0 \times 10^9$/L) was noted in 98% during their course of disease, and temporary leukopenia was detected in 64% of patients in the first week of illness [9]. The first case of SARS-CoV-2 infection confirmed in the USA developed a slight decrease in white cell count within 1 week from onset [10]. An early research of 41 patients with COVID-19 hospitalized at Jin Yin-tan Hospital showed that the blood counts of them on admission indicated leukopenia (accounted for 25%) and lymphopenia (accounted for 63%) [5]. Subsequently, in a larger sample study, only 9% of COVID-19 cases showed decreased leukocyte, while the proportion of lymphopenia was still as high as 35% [6]. Zhongnan Hospital of Wuhan University reported clinical features of 138 patients with COVID-19 and found that up to 70.3% of them developed lymphopenia with a median lymphocyte count of 0.8×10^9/L [7]. Of the 140 COVID-19 patients with blood cell test on the day of hospital admission, 75.4% of them showed lymphopenia [11]. A latest domestic research extracted the data of 1099 cases with laboratory-confirmed COVID-19 from 552 hospitals in 31 provinces/provincial municipalities in China, of which 33.7% had leukopenia ($< 4.0 \times 10^9$/L) and 82.1% had lymphopenia ($< 1.5 \times 10^9$/L) [4]. Another retrospective cohort study summarized the initial laboratory indices of patients with COVID-19 and proposed that more than half of them had lymphopenia (126 of 197, 64%) [12]. Lymphocytes, the major antiviral cells, were found to be prone to decrease continually and severely in ICU and dead patients when Zhongnan Hospital of Wuhan University kept track of the lymphocyte changes in COVID-19 patients [7]. Compared with patients without acute respiratory distress syndrome (ARDS), for patients with ARDS, the value of lymphocyte counts (difference, -0.34×10^9/mL; 95%CI, -0.47 to -0.22×10^9/mL; $p < 0.001$), $CD4^+$ (difference, -138.00 cells/μL; 95%CI, -224.00 to -51.00 cells/μL; $p = 0.004$), and $CD8^+$ T cells (difference, -66.00 cells/μL; 95%CI, -129.00 to -7.00 cells/μL; $p = 0.03$) were significantly decreased [12]. In the first COVID-19 case reported in the USA, improvement in infection-related symptoms and recovery in lymphocyte occurred almost simultaneously (about 2 weeks of illness) [10]. Peripheral blood lymphocyte count $< 0.8 \times 10^9$/L was entered in a backward stepwise logistic regression analysis to predict the mortality of virus-infected pneumonia patients (OR = 4.53, 95% CI 2.55–8.05, $p < 0.001$) [13]. The median lymphocyte count of early reported COVID-19 cases was 0.8×10^9/L, demonstrating a high proportion of severe cases or a high risk of course progression among hospitalized patients in Wuhan [5, 7].

The counts of $CD4^+$ and $CD8^+$ T cells fell early during the course of SARS, which was associated with adverse outcomes [9]. In patients infected with cytomegalovirus (CMV) and Epstein-Barr virus (EBV), the $CD8^+$ T lymphocytes increased remarkably, but $CD4^+$ T cells did not show a significant change compared with normal controls [14]. For human immunodeficiency virus (HIV) infection, $CD4^+$ T cells dropped quickly and returned to normal range in the acute phase, while $CD8^+$ T cells were prone to elevate and remain at a high level for several years [14]. In SARS cases, both $CD4^+$ and $CD8^+$ T lymphocytes declined, of which the absolute count decreased seriously than EBV, CMV, and HIV infection [14]. Lung injury model of SARS-CoV in BALB/c mice revealed the rapid kinetics of SARS-CoV replication and relative delayed type I interferon (IFN-I) expression in lungs resulting in the accumulation of pathogenic inflammatory monocyte-macrophages (IMMs), elevation of lung cytokine/chemokine levels, and vascular leakage [15]. In addition, IFN-I sensitized virus-specific T cell ($CD4^+$ and $CD8^+$) to apoptosis by upregulating Fas and Fas ligand on T cells [15].

It was manifested that the $CD4^+$ T lymphocytes were rapidly activated to be T helper (Th) 1 cells and induced inflammatory CD14 CD16 monocytes with high expression of interleukin-6 (IL-6) and accelerated the inflammation [16]. Importantly, high percentage of co-expression $Tim\text{-}3^+PD\text{-}1^+$ T subset existed both in $CD4^+$ and $CD8^+$ T lymphocytes, especially in ICU patients, which suggested T cells were in exhausted status from activation [16–18]. The peripheral blood from a dead COVID-19 patients was detected by flow cytometric and found that the counts of CD4+ and CD8+ T lymphocytes were decreased, while the proportion of HLA-DR (CD4, 3.47%) and CD38 (CD8, 39.4%) double-positive fraction was high, indicating the hyperactivated status of T cells [19]. Besides that, an elevated concentration of pro-inflammatory $CCR4^+CCR6^+$ Th17 was found in $CD4^+$ T cells and high expressions of cytotoxic granules in $CD8^+$ T cells (31.6% cells were perforin positive, 64.2% cells were granulysin positive, and 30.5% cells were double positive), which all proved the overactivation of T lymphocytes [19].

ACE2 (angiotensin converting enzyme 2) acts as the receptor to infect cells for both SARS-CoV-2 and SARS-CoV [20, 21]. ACE and ACE2 are homologues with different functions in the renin-angiotensin system (RAS), regulating blood pressure, vascular resistance, and the balance of fluid and electrolyte [22].

ACE2 negatively regulates RAS by inactivating angiotensin II (Ang II), which derived from decapeptide angiotensin I (Ang I) under the action of ACE [23]. The mouse models of acute lung injury showed that ACE2 knockout mice displayed more severe symptoms and the overexpression of ACE2 possessed protective function [24]. In mice infected with SARS-CoV, viral replication and viral spike protein were confirmed that could selectively reduce ACE2 but not ACE expression, and severe lung injury was mainly caused by high levels of Ang II due to the reduced ACE2 [24, 25].

A variety of studies has shown a possible role of ACE in regulating aspects of hematopoiesis [26]. It was demonstrated that increased expression of ACE in myeloid cells facilitated myeloid maturation and skewed myeloid differentiation to a more pro-inflammatory phenotype (myelomonocytic cells and macrophages), inhibited the development of myeloid-derived suppressor cells (MDSCs) in a tumor model and in a model of chronic inflammation induced by complete Freund's adjuvant [27].

It could be proposed that SARS-CoV-2 infection resulted in reduction of ACE2 and increased expression of ACE in myeloid precursors, which potentially facilitated myeloid maturation and made macrophages more pro-inflammatory along with reduction of the generation of MDSCs, and activated T cells, subsequently worsen immune response of target cells and consumption of T cells, especially CD4 and CD8 T cells. Furthermore, the pro-inflammatory phenotype of macrophage causes severe immune damage to the lung and other organs.

Neutrophilia

A series of COVID-19 reports suggested that ICU cases were more likely to appear neutrophilia, which is an indicator associated with disease progression [5, 7, 28]. According to the data from Jin Yin-tan Hospital, the median absolute neutrophil count (ANC) in ICU cases was 10.6 (5.0–11.8) × 10^9/L, much higher than the 4.4 (2.0–6.1) × 10^9/L in non-ICU cases (p = 0.00069) [5]. The median ANC of ICU and non-ICU patients with COVID-19 in the report of Zhongnan Hospital of Wuhan University was 4.6 (2.6–7.9) × 10^9/L and 2.7 (1.9–3.9) × 10^9/L, respectively [7]. Similar results were found in the study from Beijing Ditan Hospital; the median neutrophil count of common type was 2.4 (1.9–3.4) × 10^9/L, while the median neutrophil was higher in severe or critical type, 2.8 (2.3–4.4) × 10^9/L, (p = 0.025) [28]. A study of 69 confirmed cases of SARS-CoV-2 infection from Singapore showed that ICU patients tend to develop neutrophilia during hospitalization with a median peak ANC of 11.6× 10^9/L, compared to 3.5× 10^9/L in the non-ICU group [29]. According to a retrospective research including initial laboratory indices of COVID-19 patients, 34.5% of them demonstrated neutrophilia, and patients with ARDS (7.04, (IQR 3.98 to 10.12)) developed higher neutrophils than those without ARDS (3.06, (IQR 2.03 to 5.56)), (p < 0.001) [12]. Furthermore, among patients with ARDS, higher neutrophils were detected in those who had died [12]. Hematological parameters were tracked from day 1 to day 19 after the onset of COVID-19 at an interval of 2 days, and it was found that non-survivors developed more severe lymphocytopenia and higher neutrophils counts than survivors [7].

Risk factors associated with the composite endpoint (included admission to ICU, requirement of invasive ventilation and death) in univariate competing risk model suggested that leukocyte count more than 4000/mm^3 was a related indicator (hazards ratio, HR, 2.541; 95% confidence interval, 95%CI, 1.284–5.028; p = 0.007) [4]. Furthermore, the multivariate competing risk model showed that severe pneumonia cases (subdistribution hazards ratio, SDHR, 9.803; 95%CI, 4.06–23.67), leukocyte count more than 4000/mm^3 (SDHR, 4.01; 95%CI, 1.53–10.55), and interstitial abnormality on chest X-ray (SDHR, 4.31; 95%CI, 1.73–10.75) were related to the composite endpoint [4]. In this report, the leukocytosis might be attributed by neutrophilia, since lymphopenia developed simultaneously.

A bivariate Cox regression confirmed that neutrophilia was associated with both ARDS development (HR, 1.14; 95%CI, 1.09–1.19; p < 0.001) and progression to death (HR, 1.08; 95%CI, 1.01–1.17; p = 0.03) [12]. High neutrophil counts with activation of neutrophils possibly generate an immune response to fight with virus and contribute to the cytokine storm.

In patients with severe COVID-19, obvious lymphopenia emerged as ANC elevated concurrently. In the clinical reports mentioned above, the median lymphocyte count was 0.4 (IQR 0.2–0.8) × 10^9/L and 1.0 (IQR 0.7–1.1) × 10^9/L in ICU and non-ICU cases (p = 0.0041) in the Jin Yin-tan Hospital study and 0.8 (IQR 0.5–0.9) × 10^9/L and 0.9 (IQR 0.6–1.2) × 10^9/L in severe and common type patients (p = 0.03) in the Zhongnan Hospital [5, 7].

Then, a data of 61 cases with COVID-19 were analyzed and found that neutrophil-to-lymphocyte ratio (NLR) was a useful predictive factor for critical illness probability [28]. In this investigation, patients were divided into two groups based on the cutoff value of NLR (low risk, < 3.13; high risk, ≥ 3.13) and age (< 50 years or ≥ 50 years) [28]. Stratification for severe disease incidence was performed according to age and NLR; it was found that in the population of age ≥ 50 years, patients with high-risk NLR (50%) were prone to develop severe illness than those with low risk NLR (9.1%) (p = 0.0195) [28]. Compared with the two typical scoring models, MuLBSTA (multilobular infiltration, lymphocytopenia, bacterial coinfection, smoking history, hypertension, and age) (0.762; 95%CI, 0.585–0.938) and CURB-65 (confusion, urea, respiratory rate, blood pressure, age ≥ 65 year) (0.700; 95%CI, 0.505–0.896), NLR had a higher area under the curve (0.849; 95%CI, 0.707–0.991), which suggests that NLR works better in early prediction of the incidence of critical conditions [28].

Thrombocytopenia

In the initial 41 COVID-19 cases reported by Jin Yin-tan Hospital, thrombocytopenia (platelet count < 100×10^9/L) appeared in 5% (2/40) of them [5]. Subsequently, a 99 cases report showed 12% of them developed thrombocytopenia [6]. A large sample size study of 1099 patients with COVID-19 demonstrated a higher incidence of thrombocytopenia (platelet count < 150×10^9/L) of 36.2% [4]. Further analysis found that severe cases (57.7%) exhibited an increased susceptibility to thrombocytopenia than non-severe one (31.6%) ($p < 0.001$), and the median platelet count in severe type was markedly lower than that in non-severe type: 137.5 (IQR 99.0–179.5) × 10^9/L vs 172.0 (IQR 139.0–212.0) × 10^9/L, ($p < 0.001$) [4].

The investigation identified the lung as an organ with potential hematopoietic function and a primary site of terminal platelet production, which accounting for approximately 50% of the total platelet production [30]. On the basis of previous work proposing that the lungs are a reservoir for resident megakaryocytes and hematopoietic progenitor cells, suggesting thrombocytopenia could be caused by damage to the lungs [30]. Lung damage in COVID-19 could also induce the activation of RAS and cause abnormal functions of vascular endothelial cells and coagulation system, and platelet activation and aggregation, which might further increase consumption of platelet.

Decline of hemoglobin

Anemia was not a common laboratory finding of patients with SARS-CoV-2 infection, but the hemoglobin showed a descending tendency in fact. The first COVID-19 case in the USA showed a slight decrease in hemoglobin in illness day 6 and then recovered as the condition improved [10]. Hemoglobin was below the normal range in 51% of 99 patients with SARS-CoV-2 infection reported by Jin Yin-tan Hospital [6]. In 41 patients with COVID-19 pneumonia, the hemoglobin level of severe patients was lower, although the difference was not marked (122.0 g/L (111.0–128.0) vs 130.5 g/L (120.0–140.0), $p = 0.20$) [5]. In the study of 1099 patients with COVID-19, the hemoglobin level of 128.0 g/L (111.8–141.0) in severe group was lower than that of 135.0 g/L (120.0–148.0) in non-severe one ($p < 0.001$) [4]. It is noteworthy that the reduction of hemoglobin was more pronounced in patients who reached composite endpoint (included admission to ICU, requirement of invasive ventilation and death) than in those who did not (125.0 g/L (105.0–140.0) vs 134.0 g/L (120.0–148.0), $p = 0.012$) [4]. In the report of Zhou et al., although there was no difference in the incidence of anemia, the hemoglobin of the patients with severe cases decreased more significantly (125.42 g/L (97–144) vs 145.24 g/L (111–162), $p = 0.002$) [16].

Inflammatory changes caused by SARS-CoV-2 infection could interfere with erythropoiesis, resulting in a decrease in hemoglobin. The low incidence of anemia in COVID-19 may relate to the long life span of erythrocyte and the compensatory proliferation of erythrocyte induced by pneumonia-associated hypoxia. For COVID-19, the reduced hemoglobin levels might be an indicator of disease progression, and it would be more worthy to focus on the decline of hemoglobin level, not on anemia.

Other hematological abnormalities

Thus far, human ACE2 has been confirmed as the receptor for the entry of SARS-CoV-2 into lower respiratory tract epithelial cells [21]. The physiological balance between ACE and ACE2 is likely disrupted by SRAS-CoV-2 infection, which results in the activation of RAS and abnormal functions of vascular endothelial cells and coagulation system [25]. The common chronic medical illness complicated with severe cases of COVID-19 induced diabetes, cardiovascular and cerebrovascular diseases, which are associated with vascular endothelial dysfunction [3–7].

D-dimer elevation and prolonged prothrombin time were observed in severe COVID-19 cases [5, 7]. In the early report of Jin Yin-tan Hospital, prothrombin time (12.2 s (IQR 11.2–13.4) vs 10.7 s (IQR 9.8–12.1), $p = 0.012$) and D-dimer level (2.4 mg/L (IQR 0.6–14.4) vs 0.5 mg/L (IQR 0.3–0.8), $p = 0.0042$) on admission were higher in ICU cases than non-ICU cases [5]. The same outcome of D-dimer level was detected in Zhongnan Hospital that patients with critically condition had significantly elevated D-dimer level than common patients (414 mg/L (191–1324) vs 166 mg/L (101–285), $p < 0.001$) [7]. The difference of prothrombin time between ICU and non-ICU patients was not proposed by the research of Zhongnan Hospital (13.2 s (12.3–14.5) vs 12.9 s (12.3~13.4), $p = 0.37$) [7]. The latest study of 1099 cases with COVID-19 demonstrated that 46.4% of them had increased D-dimer levels (≥ 0.5 mg/L), and the severe patients were more prone to develop an elevation in D-dimer than non-severe patients (59.6% vs 43.3%, $p = 0.003$); the rate of D-dimer elevation was as high as 69.4% in those who reached the composite endpoint [4].

Conclusions

COVID-19 is a new human infectious disease caused by a novel coronavirus SARS-CoV-2. Hematological abnormalities are not rare in COVID-19 patients including lymphopenia, neutrophilia, thrombocytopenia, and decline of hemoglobin. A conspicuous decline was observed in $CD4^+$ and $CD8^+$ T lymphocytes. When the disease progresses to severe stage, lymphopenia continues to aggravate. Increased neotrophil

count and neutrophil-to-lymphocyte ratio, and decreased hemoglobin concentration were identified as the risk factors of severe illness in patients with SARS-CoV-2 infection. The activation of monocyte-macrophage system aggravates the immune damage of the lung and other tissues, which leads to the increase of D-dimer, prothrombin time, and platelet consumption. The effects of SARS-CoV-2 on hematopoiesis are still poorly understood, which deserves further exploration.

Author contribution All authors have made substantive intellectual contributions to this study. Guangsheng He contributed to the study design and involved in drafting and revision of the article. Xiaoqing Liu contributed to literature research and data collection and is involved in drafting. Run Zhang contributed to the data collection, analysis, and revision of the article.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Not applicable.

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