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A summary of the diagnostic and prognostic value of hemocytometry markers in COVID-19 patients

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ABSTRACT

Many studies have reported hemocytometric changes in COVID-19 infection at admission and during the course of disease, but an overview is lacking. We provide a summary of the literature of hemocytometric changes and evaluate whether these changes may assist clinicians in diagnosing and predicting disease progression of COVID-19. Eighty-three out of 250 articles from December 2019 to 20 May 2020 were included from the databases, PubMed, Web of Science Core Collection, Embase, Cochrane and MedRxiv. Our review of the literature indicates that lymphopenia and an elevated neutrophil/lymphocyte ratio are the most consistent abnormal hemocytometric findings and that these alterations may augment in the course of time, especially in those with severe disease.

Abbreviations: CRP: C-reactive protein; ICU: intensive care unit; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; MPV: mean platelet volume; NLR: neutrophil-lymphocyte-ratio; PLR: platelet-lymphocyte-ratio; PLR: platelet-lymphocyte-ratio; WBC: white blood cell count

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Introduction

The novel coronavirus pandemic, known as COVID-19 and caused by the SARS-CoV-2 virus, began in December 2019 in Wuhan, China and spread rapidly throughout the world. Knowledge of widely available diagnostic tools indicating a COVID-19 infection would help to control the pandemic. Molecular techniques to detect the virus have been developed, but healthcare workers have limited access to these tests as they require specialized equipment and expertise. Serology tests, which are even more limited, are still being evaluated and their use is more appropriate for epidemiological purpose. In daily practice, indirect indicators of COVID-19, such as increases in C-reactive protein (CRP), D-dimer, albumin, ferritin and LDH levels, are also used and have proven to be of value, especially to estimate the severity of infection. Also, hemocytometric changes have been identified as supporting evidence of a COVID-19 infection and as possible indicators of severe disease.

Several international guidelines describe that suspected SARS-CoV-2 infection shows abnormalities in hemocytometry, particularly in severe cases. In January 2020, diagnostic criteria that were published by Chinese authorities state that one of the two following criteria should be met: fever or respiratory symptoms; or normal or decreased white blood cell counts/decreased lymphocyte counts. In addition, computerized tomography-based pneumonia should be present as well as a travel history or contact with a patient with fever or respiratory symptoms from Hubei Province or with a confirmed case within 2 weeks [1]. Guidelines for Australia and New Zealand, released in March 2020, identified lymphopenia and neutrophilia as prognostic markers for severe disease in COVID-19 cases [2]. The Centers for Disease Control and Prevention in the United States also released guidance that stressed that leukopenia (9–25%), leukocytosis (24–30%), and lymphopenia (63%) were among the most common laboratory abnormalities reported in hospitalized COVID-19 patients with pneumonia [3].

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A complete blood count is the most commonly-performed hematological laboratory test worldwide and most routine laboratories are equipped with a hematology analyzer. They are often high-throughput systems providing results within a short time. Although many papers describing hemocytometric changes in COVID-19 patients, some of them peer reviewed, others not yet, are available on the Internet, an overview of the data is lacking. The primary aim of the present study is to provide a review of the literature of hemocytometric changes in adult patients with COVID-19 and to assess whether these changes have prognostic value.

Search strategy

The databases, PubMed, Web of Science Core Collection, Embase, Cochrane, MedRxiv, and Google Scholar were used as search engines and the search included the key words: "COVID," "COVID-19" "biomarker*," "coronavirus," "CBC," "SARS-COV-2," "WBC," "Lymph*," "NLR," "CD," "clinical," "hemocytometry," "laboratory," "cytokines, "immun*," "differential," "hemoglobin," "red blood cells," "monocyte*," "platelet*," "eosinophil*," "basophil*," and "complete blood count." Articles from December 2019 to 20 May 2020 that discussed cellular results of COVID-19 patients in addition to the immunopathology of the disease were included. Papers were excluded if they were not related to hemocytometry parameters in COVID-19 patients specifically, unless they provided information about pathophysiology related to other coronaviruses. At the time of inclusion, 21 papers had yet to be peer reviewed. Not included in our analysis were single case studies unless they contributed valuable new information. Studies on pediatric patients and pregnant women were included and are discussed separately as many of these studies had a small number of patients. Papers originated from China, Japan, Taiwan, Singapore, Iran, Spain and Italy, but most were from China. Populations differed in composition (genetics/lifestyle) and prevalence of co-morbidities. Some studies included in this review refer to patient results during treatment. As there is currently no specific treatment for COVID-19, this refers to supportive treatment following hospital admission.

Summary of hemocytometry markers

Approximately 250 papers met the criteria of the search terms and were reviewed. After excluding certain case studies and papers focusing only on chemistry parameters, this was reduced to a final 82 papers, including seven papers with supporting information about pathogenesis. Tables 1–4 summarizes the eleven largest studies included in this literature review, but other, smaller papers are also referenced. The 11 studies with the largest sample sizes described positive COVID-19 patients in general, severe and non-severe groups, survivors and non-survivors, and ICU and non-ICU patient groups. Smaller studies sometimes had contradictory results, which are also discussed in this paper. The findings in Tables 1–4 represent the most frequently discussed parameters reviewed in the literature, but other, less frequent, findings are also included in this paper for consideration. Table 1 summarizes white blood cell count (WBC) findings, Table 2 neutrophils and neutrophil-lymphocyte-ratio (NLR), Table 3 lymphocytes, and Table 4 platelets and platelet-lymphocyte-ratio (PLR). Most of the patients were adults over 65 years old and the eleven largest studies presented in the tables were from China. Severe and non-severe cases were categorized using criteria established by the National Health Commission of China; mild and moderate classifications were combined into the non-severe group for the purposes of consolidation and the severe group was as defined by the guideline. In the literature, either the National Health Commission of China criteria or the WHO-China Joint Mission on Coronavirus Disease 2019 was used to determine disease severity [4].

White blood cell numbers for diagnosis and prognosis

White blood cell numbers summarized in Table 1 indicate that WBC was decreased or normal in COVID-19 patients; however, in severe cases the WBC was increased when compared to the non-severe cases [5], and such an increase was even more frequent in critical patients [6]. In the largest cohort of 1099 confirmed COVID-19 patients, leukocytosis was seen in over 25% of the most severe cases [7]. Small scale studies not included in Table 1 also showed normal or decreased white blood cells upon admission, but leukocytosis was seen in some ICU patients, including 54% of 41 COVID-19 patients in one study [8]. In general, white blood cell numbers seemed to be normal or decreased in COVID-19 patients upon admission [8–15]. The same finding was observed in asymptomatic patients [16]. Also age dependency has been reported related to disease severity, and higher WBC counts were observed in elderly patients compared to younger adults with COVID-19 [17]. As the disease progressed, white blood cell numbers appeared to increase, and this was even more so in severe cases compared to non-severe cases [18]. Leukocytosis was associated with intensive care unit (ICU) admission and was more frequent in non-survivors as compared to survivors [19,20]. In contrast, Shi et al.

Table 1. Changes in white blood cell (WBC) parameters for eleven cohort studies in COVID-19 patients.

Study	Cohort size	Study period	Patient groups	Parameter results					Statistical analysis	Relevant findings
				WBC ($\times 10^9$/L)	All patients	Non-severe	Severe	p value*		
Guan et al.	1099	11 December 2019–31 January 2020	Non-severe (926) and Severe (173)	Overall >10.0 <4.0	4.7 (3.5–6.0) 58/978 (5.9%) 330/978 (33.7%)	4.9 (3.8 to 6.0) 39/811 (4.8%) 228/811 (28.1%)	3.7 (3.0–6.2) 19/167 (11.4%) 102/167 (61.1%)		Continuous variables were expressed as medians and interquartile ranges.	Upon admission, leukopenia was present in 33.7% of patients. More patients with severe disease had leukopenia than those with non-severe disease.
Qin et al.	452	10 January 2020–12 February 2020	Non-severe (166) and Severe (286)		5.3 (3.9–7.5)	4.9 (3.7–6.1)	5.6 (4.3–8.4)	<0.001	Continuous variables were described as medians and interquartile ranges (IQRs). Independent group t tests were used for the comparison of means for continuous variables that were normally distributed; conversely, the Mann-Whitney *U* test was used for continuous variables not normally distributed.	Severe cases had higher WBC counts compared to the non-severe cases ($p < 0.001$).
Huang et al.	344	25 January 2020–24 March 2020	Non-severe (299) and Severe (45)		4.8 ± 2.1	4.6 ± 1.9	5.7 ± 3.1	0.027	Continuous variables were expressed as means ± SD. The Student *t*-test was used for the comparison of normally distributed variables and the Mann-Whitney U-test for non-normally distributed variables.	Higher levels of WBC were found in the severe group compared to non-severe ($p = 0.027$).
Hu et al.	323	8 January 2020–20 February 2020	Non-severe (151) and Severe (171)†	>10.0	23/323(7.1%)	5/140(3.6%)	18/165 (10.9%)	0.009	For continuous variables, student *t*-test or Mann-Whitney test was used.	The most critical cases in the severe group had even higher percentages of leukocytosis.
Zhang et al.	221	2 January 2020–10 February 2020	Non-severe (166) and Severe (55)	Overall <3.5 3.5–9.5 >9.5	4.4(3.2–6.6) 73(33.0) 125(56.6) 23(10.4)	4.1(3.1–5.8) 62(37.3) 94(56.6) 10(6.0)	6.2(4.1–9.4) 11(20.0) 31(56.4) 13(23.6)	<0.001 0.018 0.973 <0.001	All the continuous variables were determined the normality of the distribution by Kolmogorov-Smirnov test, the normally distributed variables were described as the means ± standard deviation (SD) and the skewed distributed variables were expressed as the median and interquartile range (IQR). Normally distributed continuous variables were compared using the Student *t*-test and skewed distributed variables by using the Mann-Whitney *U* test.	Upon admission, WBC counts of 73 (33.0%) of the 221 patients showed leukopenia (white blood cell count $< 3.5 \times 10^9$/L). The severe group had increased WBC counts overall and much more frequently than in the non-severe group ($p < 0.001$).

(*continued*)

Table 1. Continued.

Study	Cohort size	Study period	Patient groups	Parameter results					Statistical analysis	Relevant findings
				WBC ($\times 10^9$/L)	All patients	Non-severe	Severe	*p* value*		
Gong et al.	189	20 January 2020-2 March 2020	Non-severe (161) and Severe (28)			4.6 (3.7, 5.6)	5.2 (4.4, 6.7)	0.03	Continuous variables were expressed as mean (standard deviation [SD]), or median (interquartile range [IQR]), as appropriate. Parametric test (*t*-test) and non-parametric test (Mann-Whitney *U*) were used for continuous variables with or without normal distribution, respectively.	WBC count in the survivors was higher than the non-survivors ($p = 0.03$).
					All patients	Non-survivors	Survivors	*p* Value		
K. Wang et al.	296	7 January 2020–11 February 2020	Non-survivors (19) and Survivors (277)			7.8 (4.7–11.9)	4.7 (3.4–6.4)	<0.001	Continuous variables presented as medians (interquartile ranges). Differences among groups were analyzed using one-way ANOVA and Kruskal-Wallis tests for normally and skewed distributed continuous variables, respectively.	WBC counts were considerably higher in the non-survivor group compared to the survivor group ($p < 0.001$).
Y. Wang et al.	344	25 January 2020–25 February 2020	Non-survivors (133) and Survivors (211)		6.2 (4.5–8.9)	9.1 (6.1–13.3)	5.3 (4.0–6.9)	<0.001	Continuous variables were expressed as medians and interquartile ranges and Mann-Whitney test was used to test for significance.	WBC counts of non-survivors were increased compared to survivors.
Zhou et al.	191	29 December 2019–31 January 2020	Non-survivors (54) and Survivors (137)	Overall <4 4–10 >10	6.2 (4.5–9.5) 32 (17%) 119 (62%) 40 (21%)	9.8 (6.9–13.9) 5 (9%) 24 (44%) 25 (46%)	5.2 (4.3–7.7) 27 (20%) 95 (69%) 15 (11%)	<0.0001 <0.0001‡ N/A N/A	Continuous and categorical variables were presented as median (IQR) and n (%), respectively. We used the Mann-Whitney *U* test, χ^2 test, or Fisher's exact test to compare differences between survivors and non-survivors where appropriate.	Leukocytosis was associated with death, with non-survivors having increased WBC counts overall ($p < 0.0001$). Survivors more frequently had leukopenia compared to non-survivors ($p < 0.0001$).
					All patients	Non-ICU	ICU			
Chen et al.	249	20 January 2020–6 February 2020	Non-ICU (227) and ICU (22)	WBC ($\times 10^9$/L)	4.71(3.80–5.86)				Continuous variables were described with mean, median, and interquartile range (IQR) values.	On admission, leukopenia was observed in 28.9% of the patients.
Cheng et al.	701	28 January 2020–11 February 2020	All positive COVID-19 patients		7.5 ± 7.5				Continuous variables were expressed as the mean ± standard deviation.	On average, patients had a WBC count within normal range upon admission.

*Two-sided P values of less than .05 were considered statistically significant. †Severe and critical patient groups were combined for the purposes of this table. ‡χ^2 test comparing all subcategories.

Table 2. Changes in neutrophil parameters for seven cohort studies in COVID-19 patients.

Study	Cohort Size	Study period	Patient groups	Parameter Results: Neutrophils and NLR	All patients	Non-severe	Severe	*p* Value*	Statistical analysis	Relevant finding
Qin et al.	452	10 January 2020–12 February 2020	Non-severe (166) and Severe (286)	Neutrophil count ($\times 10^9$/L)	3.9 (2.6–5.8)	3.2 (2.1–4.4)	4.3 (2.9–7.0)	<0.001	Continuous variables were described as medians and interquartile ranges (IQRs). Independent group *t* tests were used for the comparison of means for continuous variables that were normally distributed; conversely, the Mann-Whitney *U* test was used for continuous variables not normally distributed.	Severe cases had higher neutrophil (4.3 vs 3.2×10^9/L; $p < 0.001$) counts and higher neutrophil-to-lymphocyte ratio (NLR; 5.5 vs 3.2; $p < 0.001$).
				Neutrophil percentage, %	74.3 (64.3–83.9)	67.5 (57.8–75.8)	77.6 (68.9–86.5)	<0.001		
				NLR	4.2 (2.5–7.7)	3.2 (1.8–4.9)	5.5 (3.3–10.0)	<0.001		
Huang et al.	344	25 January 2020–24 March 2020	Non-severe (299) and Severe (45)	Neutrophil count ($\times 10^9$/L)	3.2 ± 2	3 ± 1.7	4.7 ± 3.3	< 0.001	Continuous variables were expressed as means ± SD. The Student *t*-test was used for the comparison of normally distributed variables and the Mann-Whitney *U*-test for non-normally distributed variables.	Higher levels of neutrophils and NLR were found in the severe group ($p < 0.001$ and 0.002)
				NLR	3.5 ± 4.5	2.9 ± 2.3	7.9 ± 10.1	0.002		
Hu et al.	323	8 January 2020–20 February 2020	Non-severe (151) and Severe (171)	Neutrophil count, > 75 ($\times 10^9$/L)	100/323(31%)	39/140(27.9%)	61/165 (37%)	0	For continuous variables, student *t*-test or Mann-Whitney test was used.	The most critical cases in the severe group had neutrophilia much more frequently.
Zhang et al.	221	2 January 2020–10 February 2020	Non-severe (166) and Severe (55)	Neutrophil count ($\times 10^9$/L)	3.0(1.9–5.1)	2.6(1.8–4.0)	5.4(2.8–8.4)	<0.001	The normally distributed variables were described as the means ± standard deviation (SD) and the skewed distributed variables were expressed as the median and interquartile range (IQR). Normally distributed continuous variables were compared using the Student *t*-test and skewed distributed variables by using the Mann- Whitney *U* test.	Neutrophils were significantly increased in severe patients ($p < 0.001$).

(*continued*)

Table 2. Continued.

				Parameter Results						
Study	Cohort Size	Study period	Patient groups	Neutrophils and NLR	All patients	Non-severe	Severe	*p* Value*	Statistical analysis	Relevant finding
Gong et al.	189	20 January 2020–2 March 2020	Non-severe (161) and Severe (28)	Neutrophil count ($\times 10^9$/L)		2.8 (2.0, 3.6)	3.7 (2.8, 5.2)	<0.01	Continuous variables were expressed as mean (standard deviation [SD]), or median (interquartile range [IQR]), as appropriate. Parametric test (*t*-test) and non-parametric test (Mann-Whitney U) were used for continuous variables with or without normal distribution, respectively.	Neutrophil count was higher in severe patients compared to non-severe (p <0.01).
					All patients	Non-survivors	Survivors	*p* Value		
K. Wang et al.	296	7 January 2020–11 February 2020	Non-survivors (19) and Survivors (277)	Neutrophil count ($\times 10^9$/L)		6.4 (3.2–10.0)	3.0 (2.0–4.4)	<0.001	Continuous variables presented as medians (interquartile ranges). Differences among groups were analyzed using one-way ANOVA and Kruskal-Wallis tests for normally and skewed distributed continuous variables, respectively.	Neutrophils were considerably higher in the non-survivor group than in the survivor group ($p < 0.001$).
Y. Wang et al.	344	25 January 2020–25 February 2020	Non-survivors (133) and Survivors (211)	Neutrophil count ($\times 10^9$/L)	4.7 (2.9–7.6)	8.0 (5.5–12.2)	3.7 (2.5–5.3)	<0.001	Continuous variables were expressed as medians and interquartile ranges and Mann-Whitney test was used to test for significance.	Non-survivors had a higher neutrophil count compared to survivors.

*Two-sided *p* values of less than 0.05 were considered statistically significant. †Severe and critical patient groups were combined for the purposes of this table. NLR: neutrophil-to-lymphocyte ratio.

Table 3. Changes in lymphocyte parameters for eleven cohort studies in COVID-19 patients.

Study	Cohort size	Study period	Patient groups	Parameter Results					Statistical analysis	Relevant findings
				Lymphocytes	All patients	Non-severe	Severe	*p* value*		
Guan et al.	1099	December 11, 2019–31 January 2020	Non-severe (926) and Severe (173)	Lymphocyte count ($\times 10^9$/L) <1.5	1.0 (0.7–1.3) 731/879 (83.2%)	1.0 (0.8–1.4) 584/726 (80.4%)	0.8 (0.6–1.0) 147/153 (96.1%)		Continuous variables were expressed as medians and interquartile ranges.	On admission, lymphocytopenia was present in 83.2% of the patients. Patients with severe disease had more prominent lymphocytopenia than those with non-severe disease.
Qin et al.	452	10 January 2020–12 February 2020	Non-severe (166) and Severe (286)	Lymphocyte count ($\times 10^9$/L) Lymphocyte percentage, %	0.9 (0.6–1.2) 17.5 (10.7–25.1)	1.0 (0.7–1.3) 21.4 (15.3–32.5)	0.8 (0.6–1.1) 14.1 (8.8–21.4)	<.001 <.001	Continuous variables were described as medians and interquartile ranges (IQRs). Independent group t tests were used for the comparison of means for continuous variables that were normally distributed; conversely, the Mann-Whitney *U* test was used for continuous variables not normally distributed.	Severe cases had lower lymphocyte counts. Among 452 patients who underwent laboratory examinations on admission, most of them tended to have lymphopenia and severe cases had lower lymphocytes counts (0.8 vs 1.0 $\times 10^9$/L; $p < 0.001$).
Huang et al.	344	25 January 2020–24 March 2020	Non-severe (299) and Severe (45)	Lymphocyte count ($\times 10^9$/L)	1.2 ± 0.5	1.2 ± 0.5	0.9 ± 0.4	< 0.001	Continuous variables were expressed as means ± SD. The Student *t*-test was used for the comparison of normally distributed variables and the Mann-Whitney *U*-test for non-normally distributed variables.	Lower lymphocytes numbers were seen in the severe group compared to non-severe ($p < 0.001$).
Hu et al.	323	8 January 2020–20 February 2020	Non-severe (151) and Severe (171)†	Lymphocyte count, <20 ($\times 10^9$/L)	181/323 (56%)	72/140 (51.4%)	109/165 (66%)	0	For continuous variables, student *t*-test or Mann-Whitney test was used.	Lymphopenia occurred among 83.6% of patients with unfavorable outcomes. The most critical cases in the severe group had lymphopenia much more frequently. (91.7%) compared to the less severe (61.7%).
Zhang et al.	2 January 2020–10 February 2020		Non-severe (166) and Severe (55)	Lymphocyte count ($\times 10^9$/L) <0.5 0.5–1.1 >1.1	0.8 (0.6–1.1) 39 (17.6) 124 (56.2) 58 (26.2)	0.9 (0.6–1.2) 21 (12.7) 94 (56.6) 51 (30.7)	0.7 (0.4–0.9) 18 (32.7) 30 (54.5) 7 (12.7)	<0.001 0.001 0.788 0.009	All the continuous variables were determined the normality of the distribution by Kolmogorov-Smirnov test, the normally distributed variables were described as the	On admission, 163 (73.8%) showed lymphopenia (lymphocyte count $<1.1 \times 10^9$/L). Additionally, the lymphocyte count was significantly decreased in severe patients

(*continued*)

Table 3. Continued.

Study	Cohort size	Study period	Patient groups	Parameter Results: Lymphocytes	All patients	Non-severe	Severe	*p* value*	Statistical analysis	Relevant findings
									means ± standard deviation (SD) and the skewed distributed variables were expressed as the median and interquartile range (IQR). Normally distributed continuous variables were compared using the Student *t*-test and skewed distributed variables by using the Mann- Whitney *U* test.	compared to the non-severe patients ($p < 0.001$).
Gong et al.	189	20 January 2020–2 March 2020	Non-severe (161) and Severe (28)	Lymphocyte count ($\times 10^9$/L)		1.3 (1.0, 1.8)	1.0 (0.8, 1.4)	<0.01	Continuous variables were expressed as mean (standard deviation [SD]), or median (interquartile range [IQR]), as appropriate. Parametric test (*t*-test) and non-parametric test (Mann-Whitney U) were used for continuous variables with or without normal distribution, respectively.	Lymphocyte count was higher in severe patients compared to non-severe ($p < 0.01$).
					All patients	Non-survivors	Survivors	*p* Value		
K. Wang et al.	296	7 January 2020–11 February 2020	Non-survivors (19) and Survivors (277)	Lymphocyte count ($\times 10^9$/L)		0.7 (0.5–1.0)	1.0 (0.7–1.4)	0.003	Continuous variables presented as medians (interquartile ranges). Differences among groups were analyzed using one-way ANOVA and Kruskal-Wallis tests for normally and skewed distributed continuous variables, respectively.	Lymphocyte counts were lower in the non-survivor group than in the survivor group ($p = 0.003$).
Y. Wang et al.	344	25 January 2020–25 February 2020	Non-survivors (133) and Survivors (211)	Lymphocyte count ($\times 10^9$/L)	0.9 (0.6–1.2)	0.6 (0.4–0.7)	1.0 (0.8–1.4)	<0.001	Continuous variables were expressed as medians and interquartile ranges and Mann-Whitney test was used to test for significance.	Lymphocytopenia occurred in almost 70% of patients and was predominantly found in non-survivors.
Zhou et al.	191	29 December 2019–31 January 2020	Non-survivors (54) and Survivors (137)	Lymphocyte count ($\times 10^9$/L)	1.0 (0.6–1.3)	0.6 (0.5–0.8)	1.1 (0.8–1.5)	<0.0001	Continuous and categorical variables were presented as median (IQR) and n (%), respectively. We used the Mann-Whitney *U* test , χ^2	Lymphopenia was associated with death and baseline lymphocyte count was significantly higher in survivors than non-survivors; in survivors,
				<0.8	77 (40%)	41 (76%)	36 (26%)	<0.0001		

(*continued*)

Table 3. Continued.

Study	Cohort size	Study period	Patient groups	Parameter Results					Statistical analysis	Relevant findings
				Lymphocytes	All patients	Non-severe	Severe	*p* value*		
					All patients	Non-ICU	ICU			
									test, or Fisher's exact test to compare differences between survivors and non-survivors where appropriate.	lymphocyte count was lowest on day 7 after illness onset and improved during hospitalization, whereas severe lymphopenia was observed until death in non-survivors ($p < 0.0001$).
Chen et al.	249	20 January 2020–6 February 2020	Non-ICU (227) and ICU (22)	Lymphocyte count ($\times 10^9$/L)	1.12 (0.79–1.49)				Continuous variables were described with mean, median, and interquartile range (IQR) values.	On admission, lymphopenia was observed in 47.4% of the patients.
Cheng et al.	701	28 January 2020–11 February 2020	All positive COVID-19 patients	Lymphocyte count ($\times 10^9$/L)	0.9 ± 0.5				Continuous variables were expressed as the mean ± standard deviation.	On average, patients had lymphopenia upon admission.

*Two-sided *p* values of less than 0.05 were considered statistically significant. †Severe and critical patient groups were combined for the purposes of this table.

found that mild and severe cases both had reduced numbers of WBC that were similar in value [21]. There is the question as to whether WBC numbers may be used as a prognostic parameter. Yu et al. reported that WBC counts for COVID-19 patients and healthy controls were the same in the earlier stages of hospitalization and were helpful only later in the disease course [22]. Li et al. went as far to state that WBC counts were of no prognostic value due to variability [23]. In summary, white blood cell numbers seem to be normal or decreased upon admission, and to increase with disease progression with some severe cases having leukocytosis. When leukocytosis is present, it could also be due to co-infections, to medication such as prednisone, which is known to induce leukocytosis [24], or to variability in immune response.

Neutrophilia is present in the most severe cases

Neutrophil results were present in seven out of the 11 largest studies. The data summarized in Table 2 indicates that neutrophil numbers were mostly normal in non-severe cases but were increased in severe infections. Most smaller studies not included in Table 1 drew the same conclusion but with a few exceptions. For example, several studies reported neutrophilia present in COVID-19 patients even from the early stages of hospitalization [11,22], especially in severe cases [5,18,19,25]. Hu et al. found that even within the severe group there was variability, with 87.5% of critical patients having neutrophilia [6]. Lin et al. also reported neutrophilia in some elderly patients upon admission [17]. The possibility of neutrophilia being a predictor of disease severity has been further supported by Zhang et al., who investigated 82 deaths of COVID-19 patients and showed that neutrophilia was present in 74.3% of the cases upon admission, and that it further increased to 100% in the last 24 h before death [26]. Neutrophil counts were higher in non-survivors compared to survivors [20]. This was also supported by Wang et al., who suggested that neutrophilia might be related to the cytokine storm induced by the invasion of COVID-19 [27].

In contrast to the studies reporting neutrophilia, other, smaller studies show the opposite findings. For example, Zheng et al. did not observe neutrophilia and actually found that there was a significant reduction in granulocytes in severe as compared to non-severe patients [28]. There have also been reports of normal and even decreased neutrophils in COVID-19 patients compared to healthy controls [29], but when comparing severity, WBC was much higher in severe patients [10].

Table 4. Changes in platelet parameters for seven cohort studies in COVID-19 patients.

Study	Cohort size	Study period	Patient groups	Parameter results: Platetets and PLR	All patients	Non-severe	Severe	*p* value*	Statistical analysis	Relevant findings
Guan et al.	1099	11 December 2019–31 January 2020	Non-severe (926) and Severe (173)	Platelet count ($\times 10^9$/L)	168(132–207)	172 (139–212)	137.5 (99–179.5)		Continuous variables were expressed as medians and interquartile ranges.	On admission, thrombocytopenia was present in 36.2% of patients and was more prevalent in severe patients.
				<150	315/869 (36.2%)	225/713 (31.6%)	90/156 (57.7%)			
Hu et al.	323	8 January 2020–20 February 2020	Non-severe (151) and Severe (171)†	Platelet count, <100 ($\times 10^9$/L)	16/323(5%)	4/138(2.9%)	12/165 (7.2%)	0.095	For continuous variables, student *T*-test or Mann-Whitney test was used.	The most critical cases in the severe group more frequently had thrombocytopenia.
Zhang et al.	221	2 January 2020–10 February 2020	Non-severe (166) and Severe (55)	Platelet count ($\times 10^9$/L)	175 (127–209)	175 (136–213)	169 (111–202)	0.050	All the continuous variables were determined the normality of the distribution by Kolmogorov-Smirnov test, the normally distributed variables were described as the means ± standard deviation (SD) and the skewed distributed variables were expressed as the median and interquartile range (IQR). Normally distributed continuous variables were compared using the Student *t*-test and skewed distributed variables by using the Mann- Whitney *U* test.	Platelet count in the severe group was only slightly lower than the other groups ($p = 0.05$).
Gong et al.	189	20 January 2020–2 March 2020	Non-severe (161) and Severe (28)	Platelet count ($\times 10^9$/L)		180.0 (147.0, 221.0)	167.0 (139.5, 200.0)	0.09	Continuous variables were expressed as mean (standard deviation [SD]), or median (interquartile range [IQR]), as appropriate. Parametric test (*t*-test) and non-parametric test (Mann-Whitney *U*) were used for continuous variables with or without normal distribution, respectively.	PLR was increased in severe patients compared to non-severe ($p = 0.05$).
				PLR		131.0 (96.6, 177.4)	174.8 (117.7, 210.0)	0.05		
					All patients	Non-survivors	Survivors	*p* Value		
Zhou et al.	191	29 December 2019–31 January 2020	Non-survivors (54) and Survivors (137)	Platelet count ($\times 10^9$/L)	206.0 (155.0–262.0)	165.5 (107.0–229.0)	220.0 (168.0–271.0)	<0.0001	Continuous and categorical variables were presented as median (IQR) and n (%), respectively. We used the Mann-Whitney	Survivors had a higher a platelet count than the non-survivors ($p < 0.0001$).

(*continued*)

Table 4. Continued.

Study	Cohort size	Study period	Patient groups	Parameter results					Statistical analysis	Relevant findings
				Platetets and PLR	All patients	Non-severe	Severe	*p* value*		
									U test, χ^2 test, or Fisher's exact test to compare differences between survivors and non-survivors where appropriate.	
Y. Wang et al.	344	25 January 2020–25 February 2020	Non-survivors (133) and Survivors (211)	Platelet count ($\times 10^9$/L)	189 (142–257)	159 (112–218)	211 (161–290)	<0.001	Continuous variables were expressed as medians and interquartile ranges and Mann-Whitney test was used to test for significance.	Survivors had a higher platelet count compared to non-survivors.
					All patients					
Cheng et al.	701	28 January 2020–11 February 2020	All positive COVID-19 patients	Platelet count ($\times 10^9$/L)	213 ± 94				Continuous variables were expressed as the mean ± standard deviation.	On average, patients had a platelet count within normal range upon admission.

*Two-sided *p* values of less than 0.05 were considered statistically significant. †Severe and critical patient groups were combined for the purposes of this table. PLR: platelet-to-lymphocyte ratio.

Dynamic changes of lymphocytes are most consistent

Lymphopenia was reported in all the papers summarized in Table 3. In one of the larger studies, Guan et al. showed that 83.2% of 1099 patients included had lymphopenia upon admission, and lymphopenia was even more prominent and lower in severe cases [7]. However there was some discrepancy as to whether the presence of lymphopenia remained consistent in survivors and non-survivors. Yang et al. found no significant changes in lymphopenia between survivors and non-survivors [30]. In two larger studies, lymphopenia was predominantly present in non-survivors [20,31], with Wang et al. reporting lymphopenia in 91.6% of non-survivors compared to 55.7% in survivors [31]. Many studies reported patients with both leukopenia and/or lymphopenia [8,10,12,15,16,32–34]; however, predominantly lymphopenia [11,17,33,35–43] was consistently present in adolescents, adults, and the elderly. Fan et al. and Wang et al. reported that the percentage of lymphocytes changed dynamically over the course of COVID-19 infection, that this change was more consistent than any other hematological parameter, and that more severe lymphopenia was associated with ICU admissions and non-survivors [27,44]. This was consistent with other, larger studies, as previously mentioned. Even when compared to interleukin-6 and CRP levels, the lymphocyte count was determined to be the most sensitive and reliable parameter in predicting disease severity and outcome [45]. Zheng et al. monitored blood lymphocyte percentage as the disease progressed and noted that in severe cases, it was higher than 5% at 17–19 days after the onset of the disease, while it fell below 5% just before patients passed away [46]. Flowcytometric studies were done to better understand the subsets of lymphocytes affected.

Monocyte numbers are in the normal range

For the largest studies included in this review, monocyte numbers were generally within the normal range, but could be in the lower range in the severe patients, although some studies found no differences in severe patients [10,18]. Smaller studies that compared COVID-19 patients with healthy controls showed that COVID-19 patients had a higher monocyte count compared to healthy individuals, but it was still within the normal range [22]. In regard to severity of disease, the activation of proinflammatory monocytes has also been shown to be associated with disease severity, especially in the elderly upon early diagnosis [17]. However, activated monocytes are currently not widely available as parameters on routine hematology analyzers.

Eosinophils and basophils to be combined with other prognostic factors

Compared to other parameters of the differential, there are normally very low percentages of eosinophils and basophils in healthy individuals, but decreased numbers have still been noticed in infections. Also in COVID-19, eosinopenia and basopenia were found [18,22]. Du et al. focused on eosinopenia specifically and found its presence in almost every patient who died [47]. In one study that compared COVID-19 positive patients to COVID-19 negative patients, eosinopenia was observed in 78.8% of the positive patients as compared to 35.8% of the negative patients [23]. Zhang et al. concluded that eosinopenia could be used as a reliable factor for diagnosis when combined with lymphopenia [43]. In this study, absolute counts were used and the positive COVID-19 group had an average eosinophil count of 0.02×10^9/L compared to the negative group which had 0.05×10^9/L. Although eosinopenia and basopenia have been reported, it is important to realize that this conclusion is difficult to draw with current hemocytometry equipment due to lack of sensitivity for the lower concentrations of these cell types. The mechanisms as to why these parameters tended to be reduced need to be investigated further, but they do agree with the finding of significant granulocyte reduction, as previously mentioned [28].

Dynamic changes in platelets may predict prognosis

Platelet results were reported in seven out of the eleven largest studies and are shown in Table 4. Platelet counts upon admission were generally lower in severe compared to non-severe cases [6,7]. As well, low platelet numbers were identified as a prognostic factor in multiple smaller studies that included adults and the elderly [10,22,48]. Furthermore, Zhang et al. reported platelet numbers of $<100 \times 10^9$/L in the last 24 h before death in 60% of patients [26] while Hu et al. found thrombocytopenia in 12.5% of the most critical patients, compared to 6.4% of the patients with less severe illness [6]. Low platelets numbers had already been associated with poor prognosis, as summarized by Lippi et al, who concluded that platelet counts could determine disease severity [49]. In a small study that included 30 COVID-19 patients, Qu et al. observed leukopenia upon admission, and then found that platelets first increased and then decreased in severe patients during treatment [15]. A peak in platelet numbers was noticed, especially in elderly patients and those with longer hospital stays. Apart from low platelet numbers, increased mean platelet volume (MPV) has also been documented in COVID-19 patients [22]. In summary, COVID-19 patients generally have normal or low platelet counts upon admission, but may show dynamic changes during hospitalization. This contradicts a study that investigated previous strains of coronavirus (CoV 229 and CoV OC43), which stated that the viruses had no effect on platelet counts in infected patients [50]; thus COVID-19 has different effects on platelets.

Apart from platelet numbers, the platelet-lymphocyte-ratio (PLR) has also been reported as a parameter that indicates the severity of the infection. In 30 hospitalized patients, Qu et al. described the change in PLR ($\triangle$PLR), which was the difference between PLR at admission and the maximum PLR during treatment [15]. A cutoff value for active intervention was determined to be at $\triangle$PLR >126.7. The authors showed that if the $\triangle$PLR exceeded the cutoff, there was a longer duration of hospitalization [15]. Increased PLR was also found by Gong et al. in severe patients compared to non-severe [51].

Changes in RBC parameters due to effects of impaired erythropoiesis

Erythropoietic changes using hemocytometry have been observed in COVID-19 patients. In some studies, lower concentrations of hemoglobin were reported in 41–50% of cases upon admission [19] and they were also seen in the elderly, although results were still within the normal range [17,44]. In another smaller study, Zheng et al. also found that hemoglobin decreased with disease progression [52]. The mean corpuscular volume (MCV) was also lower in adult COVID-19 patients and the mean corpuscular hemoglobin concentration (MCHC) was significantly higher compared to healthy individuals [22]. This is most likely due to a decrease in hemoglobin. Increased red cell distribution width (RDW) has also been seen in patients with COVID-19 [51].

Neutrophil-lymphocyte-ratio (NLR) may reflect the severity of inflammation

As shown in Table 2, the neutrophil-lymphocyte-ratio (NLR) seems to be consistently increased in patients with severe COVID-19. Furthermore, studies have shown the prognostic value of the NLR [53]. Smaller studies also reported a high NLR in severe cases [18,22,54,55]. Zhichao et al. noted that higher NLR upon admission was an independent predictor for severe pneumonia in COVID-19 patients [54]. A risk predictive model based on NLR and age was established by Liu et al. to improve risk stratification and management; in their study, the incidence of a severe disease course

was only 9.1% in patients with an age ≥50 years and NLR <3.13 whereas 50% of patients with an age ≥50 years and NLR ≥3.13 developed severe illness [56]. In agreement with the high NLR present in high risk groups, 94% of the 82 deceased patients with COVID-19 in the study of Zhang et al. had an NLR >5 [26]. Due to the consistency and proven importance of this ratio, elevated NLR could be used as a screening tool at admission to hospital in order to identify high risk patients [10].

In addition to the NLR, the neutrophil-to-monocyte ratio (NMR) was noted to be significantly increased in patients with pneumonia, but there is a lack of evidence in multiple studies to support this as a strong prognostic factor for COVID-19 patients [22].

Prognostic factors in pregnant women and children

Laboratory findings in pregnant women and children differ from adults, which could be a result of differences in reference ranges between these patient groups. For example, pregnant women have increased WBC counts, and lymphocyte counts decrease in the first two trimesters and increase in the third [57]. These hematological changes could affect the prediction of disease progression in COVID-19 patients. Pregnant women with COVID-19 generally did not face major complications; however severe maternal morbidity and perinatal death was observed [58]. Pregnant women with COVID-19 pneumonia have shown atypical and inconsistent WBC results, which caused difficulty in early detection [59–61]. Liu et al. found leukocytosis in 50% of pregnant women with COVID-19 [59]. This was contradicted in other studies that showed that most pregnant patients with COVID-19 upon admission actually had lower WBC counts compared to healthy pregnant women [61]. For these patients, slightly increased WBC counts were found only in the postpartum period, indicating that pregnancy may not allow the use of WBC as a prognostic factor for COVID-19, especially upon admission [60]. Pregnant women had a much higher incidence of neutrophilia, sometimes reaching 88% compared to a maximum of 14% in non-pregnant women [59]. However, some pregnant women seemed to have lower neutrophils initially, but neutrophils were increased postpartum, as seen in Li et al.; also, postpartum women with COVID-19 showed an increase in eosinophils after delivery [60]. Lymphopenia has been noted consistently in the majority of pregnant women with COVID-19 [60–63]. However, there was no significant difference in lymphopenia between pregnant and non-pregnant COVID-19 patients [59], indicating that lymphopenia could be a prognostic factor regardless of pregnancy.

In terms of symptoms and laboratory abnormalities, COVID-19 infection in children is much milder than in adults [64]. Consequently, a limited number of studies have included COVID-19 infected children. Seven studies included between 1 and 50 children with COVID-19 that specifically discussed hemocytometry parameters. Low WBC counts were reported in children with COVID-19 [64–66]. Although leukopenia, leukocytosis, and lymphopenia were frequently seen in adult cases, this was not convincingly present in the pediatric group that ranged from 2 months to 15 years [11,67]. In addition, even in severe cases of COVID-19 in children, the numbers of white blood cells, neutrophils, lymphocytes, thrombocyte and hemoglobin levels were mostly within the pediatric reference ranges or only mildly increased [68].

Ma et al., in a study on 50 children, found reduced and increased numbers of lymphocytes in 20% and 8% of cases, respectively, with 16% having thrombocytopenia and 16% having thrombocytosis [64]. The study of Tang et al., with 26 children, showed that most of the lymphocyte values increased beyond the normal range. A study by Qiu et al., in 36 children aged 0–16 years with mostly mild to moderate COVID-19, found decreased lymphocyte numbers in 31% of children and leukopenia in 19% of children, while similar percentages have been found in adult COVID-19 cases [69].

Discussion

Many studies have reported hemocytometric changes in COVID-19 infection at admission and during the course of the disease and, when possible, patients with mild/moderate and severe disease were compared. Our review of the literature indicates that lymphopenia and an increased NLR are the most consistent abnormal hemocytometric findings and that these alterations may even augment over the course of the disease, especially in those with severe disease. Lymphopenia was also noted in pregnant women with COVID-19, but this finding was less consistent in infected children. Furthermore, eosinopenia was found at presentation, while the numbers of WBC and platelets were generally normal or decreased and the number of monocytes were within the reference range.

Lymphopenia was a consistent finding and studies using flow cytometry indicated that these changes were associated with lower CD4+ and CD8+ lymphocytes [10,12,18,28,41,70,71]. Chen et al. investigated

lymphocyte subsets during recovery and found that the levels of CD4+, CD8+ T cells and B cells seemed to increase upon viral clearance [39]. Neutrophils had the tendency to increase as disease progressed; however, their increase may also have be driven by bacterial co-infections and medications such as corticosteroids. Indeed, bacterial co-infections are commonly suspected, corticosteroids are commonly used in COVID-19 patients, and their presence may affect the utility of markers such as NLR as a prognostic marker. Furthermore, viral co-infections may occur [29] and influence hemocytometry. NLR has also been found to predict disease severity in the early stages of COVID-19 infection. Liu et al. determined that the NLR was the most promising predictive factor for critical illness in the early stages of COVID-19 infection when combined with age, and that it was more predictive than neutrophil count alone [56].

Platelets are normal or decreased in non-severe patients and significantly decreased in severe patients. Severe non-COVID infections are associated with secondary thrombocytopenia, which may be a result of antibodies damaging thrombocytes or infected hematopoietic stem cells [72] leading to hematopoietic inhibition [15]. Thrombocytopenia may also be caused by increased consumption of platelets and/or decreased production of platelets in damaged lungs in severe pulmonary conditions [72]. Higher platelet turnover leads to macrothrombocytes together with increased release of young platelets that have higher volumes and, as such, may result in a high MPV as is found in COVID-19 patients. Parameters such as the percentage or absolute numbers of immature platelets may provide insight to increased platelet consumption and the capacity of the bone marrow to compensate for this loss [73]. However, data has not been reported in COVID-19 patients to date. In contrast to platelets, the MCV as well as RBC, hemoglobin, hematocrit and mean corpuscular hemoglobin (MCH) were generally low in COVID-19 patients at onset. Tian et al. determined that the MCV increased after day 8 of admission, indicating RBC recovery thereafter [74]. When recovery did not occur, MCV remained low as has been found in COVID-19 patients who died [75]. Inflammation is known to impair the function in maturing erythrocytes and this may result in hemoglobin production being impaired in severe COVID-19 cases [76], but decreases in hemoglobin may also be due to direct infection of precursor cells by the virus itself [72]. Depressed erythropoiesis can be analyzed by measuring reticulocyte numbers or reticulocyte hemoglobin content; however, no such data is available in COVID-19 patients to date. These parameters are currently under investigation in COVID-19 patients in Europe.

Although monocyte numbers do not seem to contribute to the diagnosis or prognosis of COVID-19 patients, possibly novel monocyte parameters may be relevant. Lippi et al. discussed the role of monocytes in the progression of COVID-19 by evaluating the monocyte distribution width (MDW), measured on a DxH 900 hematology analyzer (Beckman Coulter, Brea, CA, USA), and found the MDW to be increased in COVID-19 patients, especially in severe cases [77]. Of note, increased MDW has also been associated with severe non-COVID viral infections [77].

Apart from using a hematology analyzer, changes in circulating blood cells may be analyzed microscopically. Zini et al. found hyposegmented neutrophils with coarsely clumped chromatin and dark cytoplasmic granulation as well as immature granulocytes, large, hyperchromatic platelets, apoptotic cells, and hypogranular neutrophils in COVID-19 patients upon admission [78]. Following treatment with anti-viral and anti-inflammatory medications, increased numbers of atypical lymphocytes and large granular lymphocytes were observed [78]. In another study, Zhang et al. found larger, atypical, vacuolated monocytes in the peripheral blood of COVID-19 patients [79]. Although the morphology of cells can be helpful, manual differentials can be subject to a significant degree in variation between observers. Therefore, morphological results cannot be relied on solely to diagnose a COVID-19 infection but instead can help, in addition to other automated parameters, with the overall picture of disease progression. New (research) parameters on new generation hematology analyzers are better in differentiating leukocytes [80] and may detect such morphological changes. The kind of technology used is important as some technologies may mistake hyposegmented cells as bands.

Patient characteristics such as young or advanced age or pregnancy may also influence hemocytometric parameters. No gender-based differences have been described during COVID-19 infection for WBC, neutrophils, lymphocytes, and platelets [81]. For older patients (>60 years) who have more systemic symptoms, lymphopenia and thrombocytopenia are critical factors associated with disease severity and mortality [82]. Data in COVID-19 infected children is limited and seems to indicate that hemocytometric changes are less prominent compared to adults. The value of lymphopenia as a prognostic factor in children needs to be further investigated. In pregnant women lymphopenia is consistently found and may also be a prognostic factor [60–63].

Finally, data mining or machine learning could help to develop risk models of COVID-19. By using combinations of hemocytometric and other parameters, studies have shown that survival rates can be predicted with high accuracy [51,70]. It would be helpful to focus on parameters that are widely available and of low costs to assure that they can be widely implemented.

In conclusion, hemocytometric changes, especially the presence of lymphopenia and an elevated neutrophil-lymphocyte-ratio, in patients infected with SARS-CoV-2 virus may assist clinicians in diagnosing and predicting disease progression of COVID-19. Routine hemocytometric parameters that provide insight into the dynamics of platelets (immature platelet fraction) and red blood cells (reticulocyte production index), as well as new parameters of the new generation hematology analyzers, may be of added value.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

[1] Protocol on Prevention and Control of COVID-19 (Edition 6) under National Health Commission People's Republic of China, Resources. 2020. Available from: http://en.nhc.gov.cn/2020-03/29/c_78468.htm

[2] Weinkove R, McQuilten Z, Adler J, et al. Haematology & Oncology COVID-19 interim guidance version 3.0. Haematol Soc Aust New Zeal. 2020. Available from: https://www.hsanz.org.au/Haematology&OncologyCOVID-19InterimGuidanceVersion3.019thMarch2020.pdf

[3] Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Cent Dis Control. 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

[4] Aylward B (WHO); Liang W (PRC). Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). February 16–24, 2020. WHO-China Jt Mission Coronavirus Dis 2019. 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

[5] Huang J, Cheng A, Lin S, et al. Individualized prediction nomograms for disease progression in mild COVID-19. J Med Virol. 2020. DOI:10.1002/jmv.25969

[6] Hu L, Chen S, Fu Y, et al. Risk factors associated with clinical outcomes in 323 COVID-19 patients in Wuhan, China. Clin Infect Dis. 2020. DOI:10.1101/2020.03.25.20037721

[7] Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–1713.

[8] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.

[9] Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–273.

[10] Song C-Y, Xu J, He J-Q, et al. COVID-19 early warning score: a multi-parameter screening tool to identify highly suspected patients. medRxiv. 2020. DOI:10.1101/2020.03.05.20031906

[11] Lo IL, Lio CF, Cheong HH, et al. Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics of 10 patients with COVID-19 in Macau. Int J Biol Sci. 2020;16(10):1698–1707.

[12] Chen J, Qi T, Liu L, et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect. 2020. DOI:10.1016/j.jinf.2020.03.004

[13] Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265–269.

[14] Wu F, Zhao S, Yu B, et al. Complete genome characterisation of a novel coronavirus associated with severe human respiratory disease in Wuhan, China. bioRxiv. 2020. DOI:10.1101/2020.01.24.919183

[15] Qu R, Ling Y, Zhang Y-H, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with Corona Virus Disease-19. J Med Virol. 2020. DOI:10.1002/jmv.25767

[16] Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020. DOI:10.1007/s11427-020-1661-4

[17] Lin Y, Ji C, Weng W, et al. Epidemiological and clinical characteristics of 124 elderly outpatients with COVID-19 in Wuhan, China. Lancet. 2020. DOI:10.2139/ssrn.3543596

[18] Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020. DOI:10.1093/cid/ciaa248

[19] Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020. DOI:10.1515/cclm-2020-0198

[20] Wang K, Zuo P, Liu Y, et al. Clinical and laboratory predictors of in-hospital mortality in patients with COVID-19: a cohort study in Wuhan, China. Clin Infect Dis. 2020. DOI:10.1093/cid/ciaa538

[21] Shi Y, Tan M, Chen X, et al. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. medRxiv. 2020. DOI:10.1101/2020.03.12.20034736

[22] Yu H, Yu H, Yu H, et al. Total protein as a biomarker for predicting coronavirus disease-2019 pneumonia. Lancet. 2020. DOI:10.2139/ssrn.3551289

[23] Li Q, Ding X, Xia G, et al. A simple laboratory parameter facilitates early identification of COVID-19 patients. medRxiv. 2020. DOI:10.1101/2020.02.13.20022830

[24] Shoenfeld Y, Gurewich Y, Gallant LA, et al. Prednisone-induced leukocytosis. Influence of dosage, method and duration of administration on the degree of leukocytosis. Am J Med. 1981;71(5):773–778.

[25] Qian G-Q, Yang N-B, Ding F, et al. Epidemiologic and clinical characteristics of 91 hospitalized patients with COVID-19 in Zhejiang, China: a retrospective, multi-

centre case series. J Chem Inf Model. 2012;53(9):1689–1699.
[26] Zhang B, Zhou X, Qiu Y, et al. Clinical characteristics of 82 death cases with COVID-19. medRxiv. 2020. DOI:10.1101/2020.02.26.20028191
[27] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–1069.
[28] Zheng H-Y, Zhang M, Yang C-X, et al. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. Cell Mol Immunol. 2020;17(5):541–543.
[29] Ai J, Zhang HH-YH-C, Xu T, et al. Optimizing diagnostic strategy for novel coronavirus pneumonia, a multicenter study in Eastern China. medRxiv. 2020. DOI:10.1101/2020.02.13.20022673
[30] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;2600(20):1–7.
[31] Wang Y, Lu X, Chen H, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med. 2020. DOI:10.1164/rccm.202003-0736LE
[32] Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ. 2020;368(January):1–7.
[33] Zhang G, Hu C, Luo L, et al. Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China. medRxiv. 2020. 2020.03.02.20030452.
[34] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;6736(20):1–9.
[35] Ding Q, Lu P, Fan Y, et al. The clinical characteristics of pneumonia patients co-infected with 2019 novel coronavirus and influenza virus in Wuhan, China. J Med Virol. 2020. DOI:10.1002/jmv.25781
[36] Zheng Y, Huang Z, Yin G, et al. Study of the lymphocyte change between COVID-19 and non-COVID-19 pneumonia cases suggesting other factors besides uncontrolled inflammation contributed to multi-organ injury. medRxiv. 2020. DOI:10.1101/2020.02.19.20024885
[37] Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020. DOI:10.1016/j.kint.2020.03.005
[38] Liao J, Fan S, Chen J, et al. Epidemiological and clinical characteristics of COVID-19 in adolescents and young adults. medRxiv. 2020. DOI:10.1101/2020.03.10.20032136
[39] Chen X, Ling J, Mo P, et al. Restoration of leukomonocyte counts is associated with viral clearance in COVID-19 hospitalized patients. medRxiv. 2020. DOI:10.1101/2020.03.03.20030437
[40] Tabata S, Imai K, Shuichi Kawano MI, et al. Non-severe vs severe symptomatic COVID-19: 104 cases from the outbreak on the cruise ship "Diamond Princess" in Japan. medRxiv. 2020. DOI:10.1101/2020.03.18.20038125
[41] Wang Y, Wang Y, Chen Y, et al. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol. 2020;92(6):568–561.
[42] Cheng SC, Chang YC, Fan Chiang YL, et al. First case of Coronavirus Disease 2019 (COVID-19) pneumonia in Taiwan. J Formos Med Assoc. 2020;119(3):747–751.
[43] Zhang J. J, Dong X, Cao Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy Eur J Allergy Clin Immunol. 2020. DOI:10.1111/all.14238
[44] Fan BE, Chong VCL, Chan SSW, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020;95(6):1–4.
[45] Tan L, Kang X, Ji X, et al. Validation of reported risk factors for disease classification and prognosis in COVID-19: a descriptive and retrospective study. medRxiv. 2020;21(1):1–9.
[46] Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. medRxiv. 2020. DOI:10.1101/2020.03.01.20029074
[47] Du Y, Tu L, Zhu P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study. Am J Respir Crit Care Med. 2020. DOI:10.1164/rccm.202003-0543OC
[48] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–513.
[49] Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta. 2020;506:145–148.
[50] Kim JK, Jeon J-S, Kim JW, et al. Correlation between abnormal platelet count and Respiratory viral infection in patients from Cheonan, Korea. J Clin Lab Anal. 2016;30(3):185–189.
[51] Gong J, Ou J, Qiu X, et al. A Tool to early predict severe 2019-novel coronavirus pneumonia (COVID-19): a multicenter study using the risk nomogram in Wuhan and Guangdong, China. medRxiv. 2020. DOI:10.1101/2020.03.17.20037515
[52] Zheng X, Chen J, Deng L, et al. Clinical features and risk factors for the severity of inpatients with COVID-19: a retrospective cohort study. SSRN Electron J. 2020. DOI:10.2139/ssrn.3562460
[53] Yang A, Liu J, Tao W, et al. The diagnostic and predictive role of in COVID-19 patients NLR, d-NLR and PLR. Int Immunopharmacol. 2020;84:106504.
[54] Feng Z, Yu Q, Yao S, et al. Early prediction of disease progression in 2019 novel coronavirus pneumonia patients outside Wuhan with CT and clinical characteristics. medRxiv. 2020. DOI:10.1101/2020.02.19.20025296
[55] Yang P, Ding Y, Xu Z, et al. Epidemiological and clinical features of COVID-19 patients with and without pneumonia in Beijing, China. medRxiv. 2020. DOI:10.1101/2020.02.28.20028068

[56] Liu J, Liu Y, Xiang P, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med. 2020; 18(1):206.
[57] Chandra S, Tripathi AK, Mishra S, et al. Physiological changes in hematological parameters during pregnancy. Indian J Hematol Blood Transfus. 2012;28(3): 144–146.
[58] Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: a systematic review of 108 pregnancies. Acta Obstet Gynecol Scand. 2020. DOI: 10.1111/aogs.13867
[59] Liu H, Liu F, Li J, et al. Clinical and CT imaging features of the COVID-19 pneumonia: Focus on pregnant women and children. J Infect. 2020. DOI:10.1016/j.jinf.2020.03.007.
[60] Li N, Han L, Peng M, et al. Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study. medRxiv. 2020. DOI: 10.1101/2020.03.10.20033605
[61] Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020; 395(10226):809–815.
[62] Chen Y, Peng H, Wang L, et al. Infants born to mothers with a new coronavirus (COVID-19). Front Pediatr. 2020. DOI:10.3389/fped.2020.00104
[63] Liu D, Li L, Zheng D, et al. Pregnancy and perinatal outcomes of women with coronavirus disease (COVID-19) pneumonia: a preliminary analysis. AJR Am J Roentgenol. 2020. DOI:10.2214/ajr.20.23072
[64] Ma H, Hu J, Tian J, et al. Visualizing the novel coronavirus (COVID-19) in children: what we learn from patients at Wuhan Children's Hospital. 2020. Available from: https://ssrn.com/abstract=3550012
[65] Tang A, Xu W, Shen M, et al. A retrospective study of the clinical characteristics of COVID-19 infection in 26 children. Block Caving – A Viable Altern. 2020;21(1): 1–9. Available from: https://www.golder.com/insights/block-caving-a-viable-alternative/
[66] Rahimzadeh G, Ekrami Noghabi M, Kadkhodaei Elyaderani F, et al. COVID-19 infection in Iranian children: a case series of 9 patients. J Pediatr Rev. 2020. DOI:10.32598/jpr.8.2.139
[67] Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med. 2020;26(4): 502–504.
[68] Sun D, Li H, Lu XX, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. World J Pediatr. 2020. DOI:10.1007/s12519-020-00354-4
[69] Qiu H, Wu J, Hong L, et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020;2019(20): 1–8.
[70] Yan L, Zhang H, Ph D, et al. Prediction of criticality in patients with severe Covid-19 infection using three clinical features:a machine learning-based prognostic model with clinical data in Wuhan. medRxiv. 2020. DOI:10.1101/2020.02.27.20028027
[71] Yuan H, Yuan H, Yuan H, et al. A current emerging respiratory infection: epidemiological and clinical characteristics, diagnosis and treatments of COVID-19. Lancet. 2019. DOI:10.2139/ssrn.3551344
[72] Yang M, Li CK, Li K, et al. Hematological findings in SARS patients and possible mechanisms (review). Int J Mol Med. 2004;14(2):311–315.
[73] Briggs C, Kunka S, Hart D, et al. Assessment of an immature platelet fraction (IPF) in peripheral thrombocytopenia. Br J Haematol. 2004;126(1):93–99.
[74] Tian S, Zhu X, Sun X, et al. Longitudinal analysis of laboratory findings during the process of recovery for patients with COVID-19. medRxiv. 2020. DOI:10.1101/2020.04.04.20053280
[75] De La R, Phd R, Borges M, et al. Low albumin levels are associated with poorer outcomes in a case series of COVID-19 patients in Spain: a retrospective cohort study. medRxiv. 2020. DOI:10.1101/2020.05.07.20094987
[76] McCranor BJ, Kim MJ, Cruz NM, et al. Interleukin-6 directly impairs the erythroid development of human TF-1 erythroleukemic cells. Blood Cells Mol Dis. 2014; 52(2–3):126–133.
[77] Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. Clin Chem Lab Med. 2020; 2019:39–45.
[78] Zini G, Bellesi S, Ramundo F, et al. Morphological anomalies of circulating blood cells in COVID-19. Am J Hematol. 2020. DOI:10.1002/ajh.25824
[79] Zhang D, Guo R, Lei L, et al. COVID-19 infection induces readily detectable morphological and inflammation-related phenotypic changes in peripheral blood monocytes, the severity of which correlate with patient outcome. medRxiv. 2020. DOI: 10.1101/2020.03.24.20042655
[80] Chhabra G. Automated hematology analyzers: recent trends and applications. J Lab Physicians. 2018;10(1): 15–16.
[81] Li J, Zhang Y, Wang F, et al. Sex differences in clinical findings among patients with coronavirus disease 2019 (COVID-19) and severe condition. medRxiv. 2020. DOI:10.1101/2020.02.27.20027524
[82] Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8: 420–422.