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Dynamic profile and clinical implications of hematological parameters in hospitalized patients with coronavirus disease 2019

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Abstract

Objectives: As people across the world suffer from coronavirus disease 2019 (COVID-19), further studies are needed to facilitate evaluating the severity and prognosis of COVID-19 patients. In the study, we aimed to dissect the dynamic profile and clinical implications of hematological findings in hospitalized patients with COVID-19.

Methods: We retrospectively analyzed the hematological findings of 72 patients with COVID-19 admitted from January 21 to February 17, 2020. The final date of follow-up was March 20, 2020. Dynamic profile of vital hematological parameters in severe and non-severe patients was presented at different time points (day 1, 5, 7, 9, 11, 13, 15 after admission), and the correlation of hematological parameters with hospitalization time was indicated.

Results: Of 72 patients with COVID-19, lymphopenia and leukopenia occurred in 39 (54.2%) and 20 (27.8%) patients with COVID-19, respectively. Fifteen (20.8%) patients were defined as severe cases and 57 (79.2%) were non-severe cases. Compared to non-severe patients, leukocyte count, neutrophil count and neutrophil-to-lymphocyte ratio (NLR) were significantly higher, whereas lymphocyte count was declined in severe patients at each time point. A growing trend in platelet count was found in non-severe patients over the follow-up

period. In addition, a positive correlation of NLR with hospitalization time was detected from day 5 after admission.

Conclusions: Dynamic changes in vital hematological parameters from severe and non-severe patients had been characterized in the course of hospitalization. During hospitalization, NLR was found to have certain relevance to the hospitalization days and a role in forecasting disease prognosis for patients with COVID-19.

Keywords: coronavirus disease 2019; hematological parameters; hospitalization time; neutrophil-to-lymphocyte ratio; severe acute respiratory syndrome coronavirus 2.

Introduction

Since early December 2019, several cases of pneumonia of unknown etiology had been reported in Wuhan, Hubei province, China, and promptly drew much attention [1, 2]. Severe acute respiratory infection symptoms occurred in most patients, and some rapidly developed into acute respiratory distress syndrome (ARDS) and acute respiratory failure. In early January 2020, a novel coronavirus was identified from an infected patient using next-generation sequencing by the Chinese Center for Disease Control and Prevention [3], and was formally named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4]; meanwhile, the disease was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). The SARS-CoV-2 was the seventh member of the family of coronaviruses that infect humans and partly resembled severe acute respiratory syndrome coronavirus (SARS-CoV) [3, 5]. Human-to-human transmission of SARS-CoV-2 had been testified by solid evidence [6–9], resulting in rapid spread from Wuhan to other areas. Recently, the WHO had made the assessment that COVID-19 could be characterized as a pandemic, thus calling for extended research on COVID-19. Laboratory findings of patients with COVID-19 had been briefly described in previous studies [2, 9, 10], reminding the importance of laboratory characteristics for hospitalized patients with COVID-19 and necessity for

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further research. Here, we aimed to further analyze the dynamic profile of vital hematological parameters during hospitalization and their correlation with the hospitalization time of patients with COVID-19.

Materials and methods

Participants and data collection

In this retrospective study, a total of 72 patients with COVID-19 admitted to Beijing YouAn Hospital (one of the designated hospitals for COVID-19 in Beijing, China) from January 21 to February 17, 2020, were enrolled according to the coronavirus pneumonia diagnosis and treatment program (6th trial edition) issued by the National Health Commission of the People's Republic of China (<http://www.nhc.gov.cn/>). The diagnostic criteria of COVID-19 were based on positive results of sequencing or real-time reverse transcription polymerase chain reaction (real-time RT-PCR) assay of nasal or pharyngeal swab specimens. Patients with COVID-19 were defined as severe (including the critical severe type) and non-severe (including the mild and common types) cases according to the coronavirus pneumonia diagnosis and treatment program, and the criteria of clinical classification were described as follows: (1) mild type, slight clinical symptoms with no signs of pneumonia by radiologic examination; (2) common type, fever and respiratory tract symptoms appeared and pneumonia was found by radiologic examination; (3) severe type, meet any of the following: (a) tachypnea with a respiration rate ≥ 30 beats/min; (b) resting oxygen saturation $\leq 93\%$; (c) arterial partial oxygen pressure (PaO_2)/fraction of inspired oxygen (FiO_2) ≤ 300 mmHg; (d) patients whose imaging showed that the pulmonary involvement significantly aggravated by more than 50% within 24–48 h were managed as severe type; (4) critical severe type, meet any of the following: (a) respiratory failure occurred and mechanical ventilation was required; (b) shock happened; (c) patients complicated with organ failure required ICU admission. This study was approved by the Ethics Commission of Beijing YouAn Hospital (No. 2020023), and all of the patients had signed the informed consent.

The clinical data, radiological and laboratory results on admission or during hospitalization were extracted from the electronic medical records by March 20, 2020, the final date of follow-up. We selected patients with complete hematological results on day 1, 5, 7, 9, 11, 13 and 15 after admission in order to map the dynamic profile of hematological results at different time points. In addition, complete hematological results on day 1, 5 and 7 after admission, as well as the age, gender and major comorbidities, were collected to dissect their correlation with the duration of hospitalization.

Laboratory measurement and confirmation of COVID-19

Complete blood count was completed using ADVIA 2120i hematology analyzer (Siemens, Germany). Real-time RT-PCR assays for the enrolled patients were performed by Clinical Laboratory Center, Beijing YouAn Hospital, in accordance with the technical guidance

established by the WHO (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance>).

Statistical analysis

All statistical analyses were performed using SPSS software (Version 22.0, SPSS Inc). Continuous variables were expressed as the medians and interquartile ranges (IQR), as appropriate. Categorical variables were presented as counts and percentages in each category. The Mann-Whitney U test was applied to analyze continuous variables, and chi square (χ^2) and Fisher's exact tests were used for categorical variables as appropriate. Multivariate linear regression was used to analyze the correlation between multiple variables (NLR, age, gender, comorbidity) and duration of hospitalization. A p-value (two-sided) less than 0.05 was considered statistically significant.

Results

Baseline characteristics of the participants

By March 20, 2020, 15 (20.8%) of 72 patients were defined as severe cases and 57 (79.2%) were non-severe cases. Sixty-eight (94.4%) patients were discharged and four (5.6%) died. The median duration of hospitalization was 13 days (IQR, 10–18; range from 6 to 45 days). Of 72 patients with COVID-19, the median age was 49 years (IQR, 37–64) and 33 (45.8%) were men (Table 1); 37 (51.4%) had recently been to Wuhan City and 23 (31.9%) had contact with patients with COVID-19. The most common symptoms were fever (61 [84.7%]) and cough (44 [61.1%]). Less common symptoms included fatigue (18 [25.0%]), expectoration (9 [12.5%]), dyspnea (7 [9.7%]), headache (8 [11.1%]) and anorexia (8 [11.1%]). The most common comorbidities found in the infected patients included hypertension (9 [12.5%]), cardiovascular disease (6 [8.3%]) and diabetes (5 [6.9%]). Typical radiological findings on chest computed tomography (CT) were found in 58 (80.5%) patients with COVID-19 (Table 1).

Hematological findings of patients with COVID-19 on admission

Lymphopenia ($<1.1 \times 10^9/\text{L}$) and thrombocytopenia ($<125 \times 10^9/\text{L}$) occurred in 39 (54.2%) and 10 (13.9%) patients with COVID-19, respectively; 20 (27.8%) patients

Table 1: Baseline characteristics of the patients with COVID-19.

Clinical characteristics	COVID-19 (n = 72)
Age, years	49 (37–64)
Sex	
Men	33/72 (45.8%)
Women	39/72 (54.2%)
Exposure to source of transmission within 14 days	
Recently been to Wuhan	37/72 (51.4%)
Contacted patients with COVID-19	23/72 (31.9%)
Others	12/72 (16.7%)
Comorbidities	
Diabetes	5/72 (6.9%)
Hypertension	9/72 (12.5%)
Cardiovascular disease	6/72 (8.3%)
Chronic obstructive pulmonary disease	2/72 (2.8%)
Malignancy	3/72 (4.2%)
Chronic liver disease	4/72 (5.6%)
Fever	61/72 (84.7%)
Cough	44/72 (61.1%)
Fatigue	18/72 (25.0%)
Expectoration	9/72 (12.5%)
Dyspnea	7/72 (9.7%)
Pharyngalgia	5/72 (6.9%)
Anorexia	8/72 (11.1%)
Nausea	4/72 (5.6%)
Diarrhea	1/72 (1.4%)
Abdominal pain	1/72 (1.4%)
Headache	8/72 (11.1%)
Dizziness	2/72 (2.8%)
Myalgia	4/72 (5.6%)
Bilateral patchy shadows or ground glass opacity by chest CT	58/72 (80.5%)

Data are shown as median (interquartile range, IQR) and n/N (%).
 COVID-19, coronavirus disease 2019; CT, computed tomography.

with COVID-19 had leukopenia ($<3.5 \times 10^9/L$) and one (1.4%) had leukocytosis ($>9.5 \times 10^9/L$) (Table 2). Compared to non-severe patients, the median age was significantly higher (67 years [IQR, 55–76] vs. 46 years [IQR, 35–60], $p < 0.001$) and the duration of hospitalization was much longer (20 days [IQR, 14–36] vs. 13 [IQR, 11–16], $p = 0.002$) in severe patients. Leukocyte count, count and percentage of neutrophil and neutrophil-to-lymphocyte ratio (NLR) were significantly increased, whereas the count and percentage of lymphocyte and monocyte percentage were declined in severe patients ($p < 0.05$ for all). In addition, lymphopenia and thrombocytopenia were more likely to be observed in severe patients (11 [73.3%] and 4 [26.7%], respectively) compared to non-severe patients (28 [49.1%] and 6 [10.5%], respectively) (Table 2).

Dynamic profile of vital hematological parameters in patients with COVID-19

As not all the subjects in the study simultaneously had hematological results at specific time points (day 1, 5, 7, 9, 11, 13 and 15 after admission), only 17 non-severe patients and 14 severe patients with complete hematological results at these time points were selected to compare the dynamic changes in hematological results between severe and non-severe patients. Vital hematological results were displayed at different time points in Figure 1. Compared to non-severe patients, leukocyte count, neutrophil count and NLR were significantly increased (Figure 1A, B, E), while lymphocyte count was much lower (Figure 1C) in severe patients at each time point after admission.

In non-severe patients, the median count of lymphocyte was below the lower limit ($1.1 \times 10^9/L$) of normal range in the early stage of hospitalization, and reached the lower limit until day 11 after admission. Despite a slight ascent from day 13 after admission, lymphocyte count in severe patients was far below the lower limit and generally declined during the follow-up (Figure 1C). An upward trend in NLR from severe patients was observed during hospitalization, though it partly descended from day 11 after admission. Conversely, NLR in non-severe patients remained stable at a much lower level (Figure 1E).

A growing trend was found in platelet count from non-severe patients during hospitalization. The median count of platelet on day 15 ($379 \times 10^9/L$ [IQR, 310–426] vs. $166 \times 10^9/L$ [IQR, 132–232], $p = 0.008$) was obviously higher than that on day 1 after admission in non-severe patients, yet no such alteration was found in severe patients ($180 \times 10^9/L$ [IQR, 91–279] vs. $160 \times 10^9/L$ [IQR, 111–206], $p = 0.893$) (Figure 1D). Over the follow-up period, platelet count on day 11 ($278 \times 10^9/L$ [IQR, 211–348] vs. $120 \times 10^9/L$ [IQR, 66–147], $p = 0.04$) and day 15 ($379 \times 10^9/L$ [IQR, 310–426] vs. $180 \times 10^9/L$ [IQR, 91–279], $p = 0.008$) in non-severe patients was significantly higher than that in severe patients. In addition, synchronous trends were noticed in leukocyte count and neutrophil count during the follow-up (Figure 1A, B).

The correlation of dynamic NLR with duration of hospitalization

Because not all the hospitalized patients with COVID-19 had complete hematological results on day 5 and day 7 after admission, hematological results on day 1, 5 and 7 after admission were collected in only 54 patients. NLR at each of the time points (day 1, 5, 7 after admission) was

Table 2: Hematological findings of patients with COVID-19 on admission.

		Total (n = 72)	Severe (n = 15)	Non-severe (n = 57)	p-Value ^a
Age, years		49 (37–64)	67 (55–76)	46 (35–60)	<0.001
Sex					0.216
Men		33/72 (45.8%)	9/15 (60.0%)	24/57 (42.1%)	
Women		39/72 (54.2%)	6/15 (40.0%)	33/57 (57.9%)	
Duration of hospitalization, days		13 (10–18)	20 (14–36)	13 (11–16)	0.002
Laboratory parameters	Normal range				
Leukocyte count, $\times 10^9/L$	3.5–9.5	4.0 (3.5–4.9)	6.3 (3.7–7.6)	4.0 (3.4–4.4)	0.019
<3.5	–	20/72 (27.8%)	3/15 (20.0%)	17/57 (29.8%)	0.45
>9.5	–	1/72 (1.4%)	1/15 (6.7%)	0/57	0.05
Neutrophil count, $\times 10^9/L$	1.8–6.3	2.3 (1.8–3.2)	4.2 (2.2–5.8)	2.2 (1.8–2.8)	0.004
Neutrophil, %	40.0–75.0	61.4 (50.7–70.0)	72.2 (62.6–81.6)	57.2 (50.4–67.2)	0.001
Lymphocyte count, $\times 10^9/L$	1.1–3.2	1.0 (0.8–1.4)	0.8 (0.6–1.0)	1.1 (0.8–1.4)	0.038
<1.1	–	39/72 (54.2%)	11/15 (73.3%)	28/57 (49.1%)	0.094
Lymphocyte, %	20.0–50.0	28.4 (21.1–36.4)	19.1 (9.4–27.2)	30.4 (21.7–37.4)	0.003
Monocyte count, $\times 10^9/L$	0.1–0.6	0.3 (0.2–0.4)	0.3 (0.2–0.4)	0.3 (0.2–0.4)	0.667
Monocyte, %	3.0–10.0	6.4 (5.0–8.0)	6.0 (3.9–6.7)	6.7 (5.3–8.7)	0.032
Neutrophil-to-lymphocyte ratio	–	2.0 (1.4–3.3)	3.6 (2.4–9.6)	1.9 (1.3–2.9)	0.002
Lymphocyte-to-monocyte ratio	–	4.1 (2.8–5.9)	3.2 (2.0–4.7)	4.3 (2.9–6.0)	0.102
Erythrocyte count, $\times 10^{12}/L$	Male: 4.3–5.8 Female: 3.8–5.1	4.6 (4.3–4.9)	4.6 (4.4–5.0)	4.5 (4.2–4.8)	0.295
Hemoglobin, g/L	Male: 130–175 Female: 115–150	140 (130–147)	139 (133–150)	140 (130–145)	0.51
Platelet count, $\times 10^9/L$	125–350	180 (148–225)	160 (134–216)	180 (149–227)	0.515
<125	–	10/72 (13.9%)	4/15 (26.7%)	6/57 (10.5%)	0.108
Mean platelet volume, fL	8.0–12.0	9.2 (7.4–10.1)	9.7 (9.2–11.6)	9.1 (7.1–10.0)	0.017

Data are shown as median (interquartile range, IQR) and n/N (%). ^ap-Values comparing severe and non-severe patients result from χ^2 test, Fisher's exact test or Mann-Whitney U test. COVID-19, coronavirus disease 2019.

included in the multivariate regression analysis, as well as major confounding factors such as age, gender and comorbidities (Table 3). On admission, only age was found to be positively correlated with hospitalization time ($p=0.018$, adjusted $R^2=0.291$). On day 5 after admission, NLR and cardiovascular disease instead of age were positively correlated with hospitalization time ($p=0.001$ and 0.036 , respectively; adjusted $R^2=0.448$). Furthermore, NLR on day 7 after admission was still found to be correlated with hospitalization time ($p=0.014$, adjusted $R^2=0.384$).

Discussion

To date, clinical features including epidemiological, clinical, laboratory, radiological and treatment data of patients with COVID-19 had been described in many studies [2, 9–12], in which most of the laboratory findings were shown as the significant differences between severe and non-severe patients on admission, and the role of several laboratory parameters on admission in assessing the disease severity of COVID-19. Here, we mainly dissected

the dynamic profile of vital hematological results during hospitalization and their correlations with hospitalization time.

Like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [13, 14], changes in circulating blood cells were also important features in patients with COVID-19, including abnormalities in the number and function of lymphocytes. Lymphopenia on admission was reported in numerous studies, of which the proportion varied from 36.9% to 83.2% [2, 9, 15, 16]. In the study, lymphopenia was found in 54.2% of patients on admission. Lymphocyte count in severe patients was much lower compared with non-severe patients on admission and appeared more difficult to recover during hospitalization. Disturbance of the immune system including lymphopenia, imbalance of lymphocyte subgroups and cytokine storm had been found to occur in patients with COVID-19, and the extent of disturbance might be linked to the severity of COVID-19 [2, 17, 18].

NLR had become another important laboratory parameter of patients with COVID-19 due to the characteristic changes in lymphocyte count. The NLR was considered to

Figure 1: Dynamic changes in vital hematological parameters in patients with COVID-19. Timeline plots display the dynamic profile of five hematological parameters (leukocyte count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio and platelet count) in 31 hospitalized patients with COVID-19 (14 severe cases and 17 non-severe cases). Dashed lines indicate the upper or lower normal limit of each parameter. * $p < 0.05$, ** $p < 0.01$ for severe vs. non-severe patients at the same time point. ^a $p < 0.01$ for day 15 vs. day 1 after admission in non-severe patients.

Table 3: Correlation of dynamic NLR with the duration of hospitalization.

Variables	Day 1 (n = 54)			Day 5 (n = 54)			Day 7 (n = 49) ^a		
	Standardized beta	p-Value	Adjusted R ²	Standardized beta	p-Value	Adjusted R ²	Standardized beta	p-Value	Adjusted R ²
Age	0.36	0.018	0.291	0.172	0.197	0.448	−0.044	0.851	0.384
Gender	0.153	0.217		0.169	0.127		0.148	0.354	
Hypertension	0.103	0.503		0.113	0.399		0.122	0.53	
Cardiovascular disease	0.25	0.051		0.24	0.036		0.255	0.15	
Diabetes	0.022	0.879		−0.018	0.889		0.042	0.822	
NLR	0.054	0.73		0.436	0.001		0.538	0.014	

^aCase number descends to 49 due to lack of hematological results. NLR, neutrophil-to-lymphocyte ratio.

be a marker for evaluation of the progression and prognosis in patients with infection and tumors, and increased NLR indicated poor prognosis [19–21]. Similar clinical value had been proven as NLR was applied in COVID-19. Elevated NLR on admission was considered an independent risk factor for severe illness and mortality of COVID-19 patients [12, 22, 23]. Likewise, the obviously augmented difference in NLR between severe and non-severe patients during hospitalization in this study also suggested the association between NLR and disease severity or clinical course. Through multivariate analysis, we further found that only age was correlated with the hospitalization time on admission, yet the correlation of NLR with hospitalization time gradually emerged after admission, which was significantly enhanced since day 5 after admission. Therefore, our findings suggested that dynamic NLR had implications for better evaluating the hospitalization time of patients with COVID-19.

In addition, lower platelet count had been observed in patients with more severe COVID-19 [24], as reported in patients with SARS [25, 26], and thrombocytopenia was associated with an increased risk of in-hospital mortality [27]. In the study, trends in platelet count during hospitalization varied in patients with different severity of COVID-19. Platelet count in non-severe patients obviously increased in the late stage of hospitalization, whereas it still sustained a lower profile in severe patients. It was suggested that platelet count combined with lymphocyte count and IL-6 served as markers for potential progression to critical illness [28]. Thus, monitoring dynamic platelet count presumably facilitated assessing the prognosis of hospitalized patients with COVID-19.

There were several limitations in the study. First, this was a single-center study with limited cases (especially severe cases). Second, hospitalization time in non-severe patients varied from 6 to 22 days, and the median duration was 13 days (IQR, 11–16). To match the laboratory data of severe patients, non-severe patients with complete hematological data and longer hospital stay were selected; thus, the results in Figure 1 might be influenced due to the limited cases.

Conclusions

In this single-center study of 72 patients with confirmed COVID-19 in Beijing, China, dynamic changes in vital hematological parameters (leukocyte count, neutrophil count, lymphocyte count, platelet count and NLR) had been characterized in the course of hospitalization and

NLR from day 5 after admission was found to be positively correlated with the duration of hospitalization.

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Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: This study was approved by the Ethics Commission of Beijing YouAn Hospital (No. 2020023).

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