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Clinical features and hematological findings of COVID-19 patients with blood transfusion

Yanhong Zhang[1], Shangen Zheng[2], Qiang Zhou[1], Yu Zhang[1], Yao Zheng[1], Shun Wang[1*], Lei Liu[2*]

[1] *Department of Transfusion, Wuhan First Hospital, Wuhan, Hubei 430022, China;*
[2] *Department of Transfusion Medicine, General Hospital of Central Theater Command of PLA, Wuhan, Hubei 430070, China.*

ABSTRACT

This paper aims to illustrate the clinical characteristics, hematological findings, and blood transfusion information of Coronavirus disease 2019 (COVID-19) patients. Twenty-three COVID-19 patients were treated and transfused with blood products in Wuhan First Hospital from February 12 to March 20, 2020. The patients were divided into a survivor group and a non-survivor group, respectively, according to whether the patient had been discharged or died. The results demonstrated at the time of initial blood transfusion, that the non-survivor group possessed a lower platelet (PLT) than that of the survivor group (P<0.001), and PLT were below the normal range in 6 (85.7%) non-survivor group and in 2 (12.5%) survivor group (P<0.01). Over half of these patients had abnormalities in fibrinogen (FIB), activated partial thromboplastin time (APTT), prothrombin time (PT), and international normalized ratio (INR), but no significant difference was found between the non-survivor group and survivor group. The non-survivor group had a dramatically higher D-Dimers and disseminated intravascular coagulation (DIC) scores than those of the survivor group (P<0.01). Six (85.7%) non-survivors but none of the survivors had a DIC score greater than 6 (P<0.001). Fifteen (93.8%) survivors and 2 (28.6%) non-survivors were transfused with RBC (P<0.01). The non-survivors (5/7) possessed a higher proportion for using AP than the survivors (2/16). The study suggests that COVID-19 patients who undergo blood transfusion usually possess coagulation dysfunction, and DIC may be closely related to deteriorating clinical outcomes.

Keywords: COVID-19, hematological indicator, blood transfusion, clinical outcome

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1–2]. COVID-19 has led to more than forty million infections and over a million mortalities worldwide according to the COVID-19 weekly epidemiological update (WHO, Oct 20, 2020). And the number of patients infected by SARS-CoV-2 is still rapidly increasing worldwide, especially in North America, South America, Europe, and South Asia. Clinical manifestations of COVID-19 generally range from asymptomatic or very mild to severe or critical. Current evidence indicates that severe or critical illness occurs in 15.7% of cases infected by SARS-CoV-2[3], while mortality rates in different regions and countries vary from 4.3% to 14.6%.

Severe or critically ill COVID-19 patients usually possess coagulation disorders and multiple organ

*Correspondence to: Lei Liu, Department of Transfusion Medicine, General Hospital of Central Theater Command of PLA, 627 Wuluolu Rd, Wuhan, Hubei 430070, China. E-mail: liulei890207@163.com; Shun Wang, Department of Transfusion, Wuhan First Hospital, 215 Zhongshan Rd, Wuhan, Hubei 430022, China. E-mail: wang_shun6688@sina.com.

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dysfunction[4–6]. Blood component transfusion is helpful for the prevention of adverse clinical outcomes and improvement of clinical symptoms, for instance, red blood cell (RBC) products contribute to oxygen carrying capacity, while frozen plasma (FP), cryoprecipitate (CRYO), and apheresis platelet (AP) products help to improve coagulation dysfunction. However, the clinical characteristics, hematological findings, and blood transfusion information of COVID-19 patients are rarely reported. In the present study, we analyzed the clinical characteristics and laboratory findings of 23 confirmed COVID-19 patients who were transfused with blood products during hospitalization in Wuhan.

MATERIALS AND METHODS

Patients and data collection

All enrolled patients were consecutive (n=23), with a confirmed SARS-CoV-2 infection in Wuhan First Hospital from February 12 to March 20, 2020 and were transfused with blood products during hospitalization. The patients´ treatment was based on WHO interim guidance[7], and severity status and clinical outcomes of patients were determined according to the "Notice on the Issuance of Strategic Guidelines for Diagnosis and Treatment of Novel Coronavirus (2019-nCoV) Infected Pneumonia (fifth edition draft)"[8]. A patient was categorized as non-severe if all the following requirements were satisfied: ① epidemiological history; ② fever and/or other respiratory symptoms; ③ typical computed tomography (CT) image of abnormities of pneumonia caused by SARS-CoV-2; ④ positive result in reverse transcription polymerase chain reaction (RT-PCR) for viral RNA. A patient was categorized as severe if any of the bellow clinical manifestations additionally appeared: ① respiratory rate 30/min; ② oxygen saturation ⩽ 93%; and ③ arterial partial pressure of oxygen (PaO_2) / fraction of inspired oxygen (FiO_2) ⩽ 300 mmHg (1 mmHg=0.133 kPa). The study was approved by the Hospital Ethics Committee, and oral informed consent was obtained from each patient.

Baseline information (age, sex, initial symptoms, and coexisting disorders), clinical (disease conditions and use of blood products) and laboratory data (routine blood test and coagulation function test) at the time of initial blood transfusion were extracted from electronic medical records. For the routine blood test, the parameters of neutrophils (NEUT, normal range 1.8×10^9/L–6.3×10^9/L), lymphocytes (LYMP, normal range 1.1×10^9/L–3.2×10^9/L), platelet count (PLT, normal range 125×10^9/L–350×10^9/L), and hemoglobin concentration (Hb, normal range 130–175 g/L) were analyzed. For the coagulation function test, the parameters of fibrinogen (FIB, normal range 2–4 g/L), activated partial thromboplastin time (APTT, normal range 28–44 s), prothrombin time (PT, normal range 11.5–14.5 s), thrombin time (TT, normal range 14–20 s), international normalized ratio (INR, normal range 0.8–1.2), and D-Dimers (D-D, normal range 0–1 mg/L) were analyzed. All tests were performed in accordance with the manufacturer´s instructions. The disseminated intravascular coagulation (DIC) score was assessed according to the primary disease inducing DIC, clinical manifestations, and laboratory indicators. If the score was greater than 6, it was diagnosed as DIC[9]. The enrolled patients were divided into two groups, the survivor group and the non-survivor group, respectively, according to whether the patient was discharged or died. The demographics, clinical characteristics, and laboratory data of these two groups were compared and analyzed.

Statistical analysis

Continuous variables were described as the means and standard deviations or medians and interquartile ranges (IQR) values. Categorical variables were expressed as the counts and percentages. Independent group t tests were applied to continuous variables that were normally distributed; otherwise, the Mann–Whitney test was used. Categorical variables were compared using chi-square tests, while the Fisher exact test was used when the data were limited. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS), version 22.0 software. A two-sided α of less than 0.05 was considered statistically significant.

RESULTS

Demographics and clinical characteristics

The demographics and clinical characteristics of these patients enrolled in this study were shown in ***Table 1***. The average age was 74.7 years (ranged from 57.0 to 87.0 years), and 11 (47.8%) of the patients were male. The most common initial symptoms were fever [17 (73.9%)], dry cough [14 (60.9%)], and fatigue [9 (39.1%)]. Cardiovascular and cerebrovascular disease [11 (47.8%)], hypertension [9 (39.1%)], and diabetes [7 (30.4%)]were the most common coexisting disorders. All were severe cases, and the average time from illness onset to admission, initial blood transfusion, and discharge or death were 10.4, 28.6, and 39.8 days, respectively. In addition, the median hospital length-of-stay was 33.0 days (IQR, 22.0–34.0).

Table 1 **Demographic and baseline characteristics of 23 enrolled patients with COVID-19**

Characteristics	All patients(n =23)	Survivor group(n =16)	Non-survivor group(n =7)	P value
Age (years)	74.7±7.9	75.0±8.4	73.9±7.0	0.757
Sex[n(%)]				
Male	11 (47.8)	9 (56.2)	2 (28.6)	0.371
Female	12 (52.2)	7 (43.8)	5 (71.4)	
Signs and symptoms[n(%)]				
Fever	17 (73.9)	11 (68.8)	6 (85.7)	0.621
Dry cough	14 (60.9)	10 (62.5)	4 (57.1)	>0.99
Fatigue	9 (39.1)	6 (37.5)	3 (42.9)	>0.99
Chest tightness	5 (21.7)	4 (25.0)	1 (14.3)	>0.99
Dyspnea	2 (8.7)	1 (6.3)	1 (14.3)	0.526
Chill	2 (8.7)	1 (6.3)	1 (14.3)	0.526
Sore throat	2 (8.7)	2 (12.5)	0 (0.0)	>0.99
Muscle soreness	1 (4.4)	1 (6.3)	0 (0.0)	>0.99
Nausea	1 (4.4)	1 (6.3)	0 (0.0)	>0.99
Coexisting disorders[n(%)]				
Cardiovascular and Cerebrovascular disease	11 (47.8)	7 (43.8)	4 (57.1)	0.667
Hypertension	9 (39.1)	5 (31.3)	4 (57.1)	0.363
Diabetes	7 (30.4)	6 (37.5)	1 (14.3)	0.366
Chronic respiratory disease	5 (21.7)	4 (25.0)	1 (14.3)	>0.99
Hepatopathy	5 (21.7)	3 (18.8)	2 (28.6)	0.621
Malignancy	2 (8.7)	2 (12.5)	0 (0.0)	>0.99
Nephropathy	2 (8.7)	2 (12.5)	0 (0.0)	>0.99
Disease severity status[n(%)]				
Non-severe	0 (0.0)	0 (0.0)	0 (0.0)	>0.99
Severe	23 (100.0)	16 (100.0)	7 (100.0)	
Time from illness onset to				
Admission(d)	10.4±7.2	10.9±8.1	9.4±5.1	0.713
initial blood transfusion(d)	28.6±10.4	30.1±10.4	25.3±10.2	0.349
discharge or death(d)	39.8±12.1	44.4±10.3	29.3±9.6	0.005
Hospital length-of-stay(d)	33.0 (22.0–34.0)	33.0 (33.0–34.8)	19.9±5.6	0.001

Data are mean and standard deviation ($\bar{x} \pm s$) or [n (%)]. P values comparing patients in the survivor group and in the non-survivor group are from t test, χ^2 test, Fisher´s exact test, or Mann-Whitney U test.

The enrolled patients were divided into two groups: the survivor group and the non-survivor group, respectively (***Table 1***). No statistical differences were found in baseline characteristics of these two groups patients (P>0.05). However, the non-survivors evidently had a shorter hospital stay and a shorter time from symptoms onset to clinical endpoint (discharge or death) compared with survivors (P<0.05).

Hematological laboratory findings

The hematological laboratory findings of these patients at the time of initial blood transfusion were shown in ***Table 2*** and ***Fig. 1***, and the differences be–tween the survivors and non-survivors were compared. For routine blood test, 19 patients (82.6%) had NEUT above the normal range and LYMP below the normal range. The two groups had similar proportions of NEUT above the normal range and LYMP below the normal range. However, the non-survivors possessed a higher NEUT (13.51×10^9/L *vs*. 8.43 $\times10^9$/L, P<0.05) and a lower LYMP (0.53×10^9/L *vs*. 0.88 $\times10^9$/L, P<0.05) than the survivors. PLT were below the normal range in 6 non-survivors (85.7%) and in 2 survivors (12.5%) (P<0.01). Moreover, the non-survivors possessed a much lower average PLT (68.86×10^9/L *vs*. 218.00×10^9/L, P<0.001) than the survivors. All the patients had Hb below the normal range. And the non-survivors possessed a higher Hb (98.29 *vs*. 85.5 g/L, P<0.05) compared with the survivors. For the coagulation function test, more than half of the enrolled patients had abnormalities in the values of FIB, APTT, PT, and INR. However, the values of FIB, APTT, PT, TT, and INR and the proportions of abnormalities in these indicators were not significantly different between the two groups. The average values of APTT, PT, and INR of non-survivors were higher than the upper limit of normal range. Importantly, the average value of D-D of the non-survivors was dramatically higher than that of the survivors (17.21 *vs*. 6.62 mg/L; P<0.01). And D-D values were above the normal range in 7 non-survivors (100.0%) and in 15 survivors (93.8%). In addition, a DIC score was calculated according to these hematological indicators and clinical symptoms. The non-survivors had a significantly higher DIC score compared

Table 2 **Laboratory findings of 23 enrolled patients with COVID-19**

Parameters	All patients (*n*=23)	Survivor group (*n*=16)	Non-survivor group (*n*=7)	*P* value
Routine blood test				
NEUT ($\times10^9$/L)	9.78±4.72	8.43±3.09	13.51±6.09	0.014
Increased[n(%)]	19 (82.6)	12 (75.0)	7 (100.0)	0.273
LYMP ($\times10^9$/L)	0.78±0.37	0.88±0.38	0.53±0.22	0.032
Decreased[n(%)]	19 (82.6)	12 (75.0)	7 (100.0)	0.273
PLT ($\times10^9$/L)	172.61±101.72	218.00±70.68	68.86±85.98	0.000
Decreased[*n*(%)]	8 (34.8)	2 (12.5)	6 (85.7)	0.002
Hb (g/L)	89.39±16.81	85.5±18.83	98.29±4.07	0.019
Decreased[*n*(%)]	23 (100.0)	16 (100.0)	7 (100.0)	>0.99
Coagulation function test				
FIB (g/L)	3.93±1.52	4.21±1.49	3.30±1.49	0.192
Increased or decreased[*n*(%)]	14 (59.6)	12 (75.0)	4 (57.1)	0.626
APTT (s)	39.98±18.05	37.76±11.38	45.06±28.78	0.385
Increased or decreased[*n*(%)]	12 (52.2)	8 (50.0)	4 (57.1)	0.176
PT (s)	14.25±2.59	13.94±2.47	14.96±2.93	
Increased or decreased[*n*(%)]	13 (56.5)	9 (56.3)	4 (57.1)	>0.99
TT (s)	16.80 (14.80–19.00)	16.70 (14.18–17.18)	19.00 (14.80–19.60)	0.332
Increased or decreased[*n*(%)]		6 (37.5)	1 (14.3)	0.366
INR	1.21±0.23	1.16±0.20	1.32±0.28	0.137
Increased[*n*(%)]	12 (52.2)	7 (43.8)	5 (71.4)	0.371
D-D (mg/L)	8.63±7.62	6.62±6.60	17.21±9.45	0.008
Increased[*n*(%)]	22 (95.7)	15 (93.8)	7 (100.0)	>0.99
DIC score	4.00 (2.00–7.00)	2.00 (2.00–4.00)	7.00 (7.00–8.00)	0.000
Increased[*n*(%)]	6 (26.1)	0 (0.0)	6 (85.7)	0.000

Data are mean and standard deviation ($\bar{x} \pm s$) or median (IQR). *P* values comparing patients in the survivor group and in the non-survivor group are from *t* test, χ^2 test, Fisher´s exact test, or Mann-Whitney *U* test. Survivor: patients in the survivor group. Non-survivor: patients in the non-survivor group. NEUT: neutrophils, normal range 1.8×10^9/L –6.3×10^9/L. LYMP: lymphocytes, normal range 1.1×10^9/L –3.2×10^9/L. PLT: platelet count, normal range 125×10^9/L –350×10^9/L. Hb: hemoglobin concentration, normal range 130–175 g/L. FIB: fibrinogen, normal range 2.00–4.00 g/L. APTT: activated partial thromboplastin time, normal range 28.00–44.00 s. PT: prothrombin time, normal range 11.50–14.50 s. TT: thrombin time, normal range 14.00–20.00 s. INR: international normalized ratio, normal range 0.80–1.20. D-D: d-dimers, normal range 0.00–1.00 mg/L. DIC score: disseminated intravascular coagulation score, normal range 0–6.

with the survivors (*P*<0.001). Six non-survivors (85.7%) had a DIC score greater than 6, while none of the survivors possessed a DIC score greater than 6. There results demonstrated that most of the non-survivors already had the clinical manifestations of DIC at that time.

Blood product transfusion

The causes and purposes of blood transfusion and use of blood products in these patients during the whole course were shown in ***Table 3*** and ***Fig. 2***. None of the survivors had obvious bleeding manifestations at the time of initial transfusion, while 3 non-survivors (42.9%) bled in the locations of alimentary canal and/or trachea. Ten survivors (62.5%) and 6 non-survivors (85.7%) were transfused with blood products due to abnormal hematological indicators, including decreased PLT and Hb, prolonged APTT and PT. All the survivors and 6 non-survivors (85.7%) were transfused with blood products in order to improve clinical symptoms such as dyspnea and chest tightness caused by hypoxia, skin petechia and ecchymosis or bleeding. In addition, blood products were infused in 4 survivors (25.0%) for ensuring the security of invasive operation. Of these patients, the most and least commonly used blood products were respectively RBC (17/23) and CRYO (3/23). Interestingly, 15 survivors (93.8%) were transfused with RBC, while only 2 non-survivors (28.6%) were transfused with RBC, a difference of which was statistically significant (*P*<0.01). On the contrary, the non-survivors (5/7, 71.4%) possessed a higher proportion in using AP compared with the survivors (2/16, 12.5%). No differences were found in the proportions of using FP and CRYO between the two groups. Moreover, no adverse reactions of blood transfusion were found among these patients.

DISCUSSION

In this study, the clinical features and hematological findings of 23 confirmed cases with COVID-19 at the time of first use of blood products, and blood transfusion data over the whole course of treatment were analyzed. All these cases were severe, and 21 of them (91.3%) were critically ill. This result demonstrated that these patients were very sick when

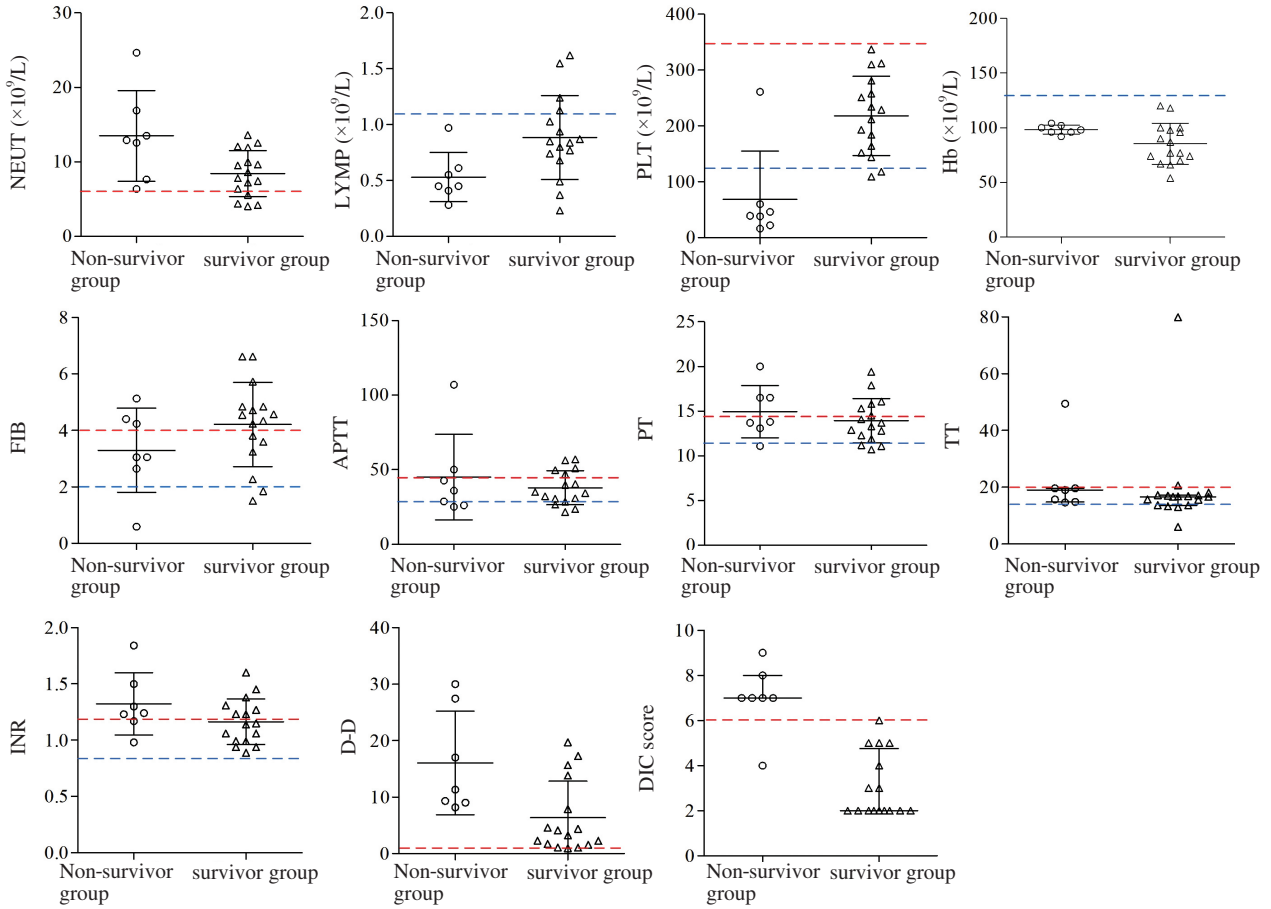

Fig. 1 **Differences of hematological indicators between non-survivors and survivors.** The values of several hematological indicators were shown and compared between non-survivors (circular) and survivors (regular triangle). The red dotted line indicates the upper limit of the normal value range, while the blue dotted line indicates the lower limit of the normal value range.

Table 3 **Laboratory findings of 23 enrolled patients with COVID-19**

Group	Patient ID	Blood group	Bleeding location	RBC (U)	FP (mL)	CRYO (U)	AP (therapeutic dose)
Survivor group	1	B	N	4	N	N	N
	2	O	N	10	600	1	N
	3	B	N	2	N	N	N
	4	A	N	10	N	N	N
	5	O	N	26	3 800	N	5
	6	AB	N	9.5	1 400	N	N
	7	A	N	2	N	N	N
	8	A	N	8	N	N	N
	9	O	N	8	1 000	22.75	N
	10	AB	N	6	N	N	N
	11	O	N	N	200	N	N
	12	A	N	8	300	N	N
	13	A	N	2	N	N	N
	14	AB	N	19.5	1 100	N	1
	15	A	N	2	100	N	N
	16	O	N	2	N	N	N
Non-survivor group	17	A	N	N	800	10	1
	18	A	N	N	900	N	N
	19	O	N	N	850	N	N
	20	AB	alimentary canal and tra–chea	2	1 000	N	6
	21	B	N	2	1 200	N	4
	22	AB	trachea	N	N	N	1
	23	O	alimentary canal	N	N	N	1

RBC: red blood cell. FP: frozen plasma. CRYO: cryoprecipitate. AP: apheresis platelet. N: none.

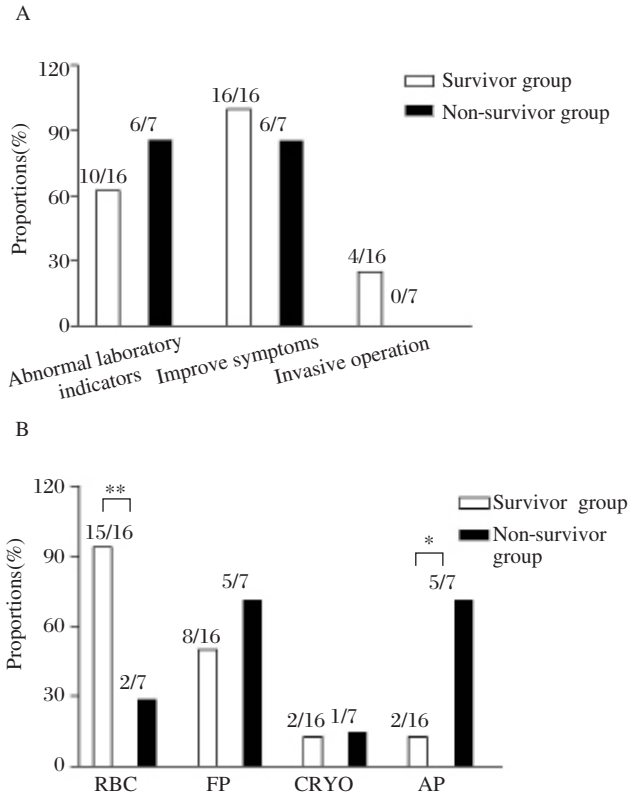

***Fig. 2* Information on the blood transfusion of survivors and non-survivors.** A: Analysis of the causes and purposes of blood transfusion. The proportions of causes and purposes of blood transfusion in survivors (white column) and non-survivors (black column) were shown. B: Information on the use of blood products. The proportions of use of blood products in survivors (white column) and non-survivors (black column) were shown. * $P<0.05$. ** $P<0.01$.

transfused with blood products. Many of the enrolled patients had abnormal hematological findings at the time of initial transfusion, including decreased PLT and Hb, increased or decreased FIB, APTT, and PT, and dramatically elevated D-D, suggesting that most COVID-19 patients that undergo blood transfusion possess coagulation disorders. Of these patients, RBC was the most commonly used blood product for improving decreased Hb and clinical symptoms of hypoxia. More than half of these patients (13/23) were infused with FP for correcting coagulation disorders and expanding blood volume. Some of these patients (7/23) were infused with AP for improving significantly decreased PLT and controlling bleeding. A few cases (3/23) with evidently prolonged APTT and decreased FIB were infused with CYRO for the supplement of endogenous coagulation factors and high concentration of fibrinogen.

In order to understand the relationship between clinical outcomes with hematological indicators and the use of blood products, enrolled patients were divided into the survivor group and the non-survivor group. LYMP and D-D are reported to be the two important laboratory indicators responsible for disease progression[4,10–12]. In this study, the non-survivors had a much lower LYMP but a significantly higher D-D than the survivors, indicating that disease seriousness for non-survivors was notably worse than those of the survivors at the time of first blood transfusion, although all the patients were severe cases even critically ill. In addition, the values and proportions of outliers of FIB, APTT, and PT were not statistically different between the two groups. However, the non-survivors´ DIC score was much higher than that of the survivors. And 6 non-survivors (85.7%) had a DIC score greater than 6, suggesting that the non-survivors already had the clinical manifestations of DIC at the time of initial blood transfusion, which may be closely related to their poor clinical outcome (death)[4,13]. None of the survivors possessed a DIC score greater than 6, but a higher DIC score also implies that patient has a more significant coagulation dysfunction. The differences of DIC score between the two group patients can be explained by that the more significantly elevated D-D and decreased PLT found in non-survivors lead to a remarkable increase in DIC score. Therefore, PLT and D-D can be the two important hematological parameters that are related to clinical outcomes of COVID-19 patients and are worthy of careful attention.

PLT was significantly decreased in the non-survivors compared with that in the survivors, which is also the main cause of a higher proportion of non-survivors using AP. The remarkably reduced PLT in non-survivors may be due to: ① consumptive coagulation leading to platelet depletion; ② binding to various viruses and inducing platelet clearance[14]; ③ cytokine storm mechanism being more plausible for decreased platelet synthesis[15]. However, the detailed mechanism needs to be studied in further depth in the future. Although Hb was decreased both in survivors and non-survivors, the average Hb of non-survivors was conversely a little higher than that of the survivors. This suggests that Hb decrease may not be closely related to adverse outcomes. Some of the non-survivors had a small amount of bleeding in the locations of alimentary canal and trachea. Generally, COVID-19 induced bleeding manifestations are much less frequent than thrombotic manifestations[16]. Taking all the above into consideration, it can be observed that COVID-19 patients with blood transfusion usually possess coagulation disorders, and DIC may be an important factor which may relate to adverse clinical

outcomes. PLT and D-D are two important hematological indicators that need to be regularly monitored. Thus, accurate diagnosis of coagulation function and timely treatment of coagulopathy are helpful for preventing the deterioration of disease conditions and improving unfavorable outcomes. However, whether blood transfusion is related to the clinical outcome of COVID-19 patients remains to be further studied.

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