

# Association of the Anemia and COVID-19 in Hospitalized Patients

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## Research Article

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## Abstract

Coronavirus disease 2019 (COVID-19) has become an extensive pandemic worldwide since it is firstly broken out in Wuhan in December 2019. As of July 26, 2020, this disease has resulted in more than 600,000 of death and the numbers remains increasing. Pneumonia is commonly developed in COVID-19 confirmed patients, and it weakens lung functions and decreases the oxygen levels of blood. As an oxygen carrier, hemoglobin transport oxygen from lung to other organs and meanwhile plays a vital role in maintaining the balance of blood oxygen. Therefore, we speculate that a decrease of hemoglobin, also known as anemia, would weaken the oxygen transport and aggravates the illness of COVID-19. Moreover, anemia is commonly observed in a large proportion of COVID-19 confirmed patients. Taken together, anemia might be associated with the COVID-19. The aim of this study was performed to evaluate the clinical characteristics of COVID-19 confirmed patients with anemia and to further investigate the relationship between anemia and COVID-19.

## Introduction

Coronavirus disease 2019 (COVID-19), which is caused by a newly discovered positive-sense single-stranded RNA virus that termed SARS-CoV-2, has become an extensive pandemic worldwide since it is firstly broken out in Wuhan, Hubei Province in December 2019.<sup>1–2</sup> As of July 26, 2020, there were approximately 15,785,000 COVID-19 confirmed cases that existed in 215 countries or regions around the world, and nearly half of them were distributed in America, Brazil and India.<sup>3</sup> Dramatically increased cases of COVID-19 lead to overwhelming of medical resources and brings huge challenges to global public health.<sup>4</sup> Up to now, COVID-19 has resulted in 640,016 of deaths due to the acute respiratory failure or other associated complications, and the number of death globally remains rapidly increasing.<sup>3</sup>

In COVID-19 confirmed patients, the developed pneumonia weakens the lung function, which persistently provides oxygen to blood through breathing and gas exchange.<sup>5–7</sup> When the illness deteriorates, oxygen levels in blood drop and the oxygen supply of tissues is impaired, leading to further tissue damage, multiple organ failure, and even death.<sup>8</sup> In most cases, high-throughput oxygen supply via nasal tubes was conducted to elevate partial pressure of arterial oxygen ( $\text{PaO}_2$ ), therefore alleviating the anoxia of patients. As is well-known, hemoglobin acts as an oxygen carrier, which combines oxygen at lung tissues and releases oxygen in various organs, meanwhile plays a vital role in maintaining the balance of blood oxygen and the level of  $\text{PaO}_2$ .<sup>9</sup> Therefore, a decrease of hemoglobin in COVID-19 patients, also known as anemia,<sup>10</sup> was speculated to weaken the capability of oxygen delivery and to aggravate the illness. Although the understanding of COVID-19 has been greatly enhanced in a very short period of time,<sup>11–15</sup> the association between the anemia and COVID-19 is yet unclear. The aim of this study was to determine the clinical characteristics of COVID-19 confirmed patients with anemia and to further explore the relationship between anemia and COVID-19.

## Methods

# **Study design**

A retrospective research was conducted by using data of the electronic medical records system. The study was approved by the Wuhan Union Hospital of Huazhong University of Science and Technology institutional review board and informed consent were waived. All experiments were performed in accordance with the relevant guidelines and regulations of this institutional review board. In this study, we enrolled 162 of COVID-19 confirmed patients who were admitted to Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, from February 13 to March 17. Among these patients, 25 of patients were excluded due to incomplete medical records (23 cases) and lack of positive RT-PCR results (2 cases). Ultimately, a total of 137 patients were included in this cohort.

In accordance with official treatment and management policy, all the costs of COVID-19 treatments were free, and all the patients with severe or critical illness were admitted into the designated hospitals for treatments. In addition, the mild patients and a most part of ordinary patients were treated in the cabin hospitals. In this study, we enrolled three types of patients, including ordinary, severe and critical patients. The COVID-19 cases were confirmed by positive RT-PCR results, replenishing with ground-glass opacities in chest CT. All cases in this study were reviewed by three physicians (CC, WZ and ZL) under the COVID-19 Diagnosis and Treatment Guideline issued by the National Health Committee of China (7th Edition) and the World Health Organization interim guidance.

## **Data collection**

Data of this retrospective study were from union hospital. Chart records of all the patients were carefully checked by three physicians, respectively. The medical data, such as demographics, presence of underlying diseases (anemia, hypertension, diabetes, cardiovascular diseases, cerebrovascular diseases, malignant tumors and so on), clinical characteristics, laboratory results, CT imaging results and the disease conditions were collected from the electronic medical records.

The real-time RT-PCR was designed to amplify ORF1ab and N genes of SARS-CoV-2 using a commercial detection kit (BioGerm, Shanghai, China) in the Nucleic acid testing laboratory, Department of clinical laboratory, Wuhan Union Hospital. A double-positive result and two consecutive single-positive results were termed positive RT-PCR results. The other laboratory results, such as hemoglobin (Hb), C reactive protein (CRP), lactate dehydrogenase (LDH) and lymphocyte counts were also acquired from the department of clinical laboratory.

## **Definitions**

The anemia in adults was defined as followings: (1) mild: the Hb levels in whole blood of patients was below 120 g/L in males, 110 g/L in females or 100 g/L in pregnant women; (2) moderate: the Hb levels in whole blood of patients was equal to or below 90 g/L while over 60 g/L; (3) severe: the Hb levels in whole blood of patients was equal to or below 60 g/L while over 30 g/L; (4) critical: the Hb levels in whole blood of patients was equal to or below 30 g/L.

According to the COVID-19 Diagnosis and Treatment Guideline issued by the National Health Committee of China (7th Edition), we classified the COVID-19 patients in this study with ordinary, severe and critical illness: (1) ordinary: patients developed the common symptoms, including fever, cough, sore throat and so on, while having typical ground-glass opacities but no signs of severe pneumonia; (2) severe: patients met one of the following criteria: respiratory distress, respiratory rates over 30 times per minute, blood oxygen saturation below 93% at rest, or ground-glass lesions aggravating beyond 50% within 48 hours; (4) critical: patients met one of the following criteria: respiratory failure, requiring mechanical ventilation, shock, or multiple organs failure.

The patients must meet the following requirements before being discharged from the hospital: (1) maintaining normal temperature for more than 3 days; (2) two consecutive negative RT-PCR results (every two sampling intervals must be more than 24 hours); (3) obvious improvement of clinical symptoms; (4) significant improvement of pulmonary inflammation on CT imaging.

## Statistical analysis

All data were documented in excel file and analyzed using SPSS software (version 21). Continuous variables were expressed as median (IQR), and categorical counterparts were presented as n (%). We performed the *t*-test and  $\chi^2$  test to compare differences in continuous data and categorical data, respectively. Certain risk factors, such as male, age, underlying disease, CRP, d-dimer, lymphocyte and so on, were reportedly associated with severity and clinical outcome of COVID-19. We included these variables and anemia into the model and then determined the independent risk factors using multivariable logistic regression analysis.

## Results

### Basic characteristics

After excluding 23 patients that have incomplete medical records and two inpatients without being confirmed by SARS-CoV-2 RT-PCR assay, we enrolled a total of 137 incident cases of COVID-19 who were admitted to Wuhan Union Hospital from February 13 to March 17. Among them, 67.9% (93 cases) were ordinary patients, 17.5% (24 cases) were severe and 14.6% (20 cases) were critical ill. The median age of the 114 COVID-19 patients was 60 years (IQR 49.0–70.0), ranging from 20 years to 93 years, and 58.4% were male. The most common symptoms of patients are fever (67.9%), cough (50.4%), fatigue (24.1%) and dyspnoea (23.4%), followed by chest congestion (15.3%), sputum production (12.4%), muscle soreness (10.9%) and diarrhea (7.3%). A little proportion of patients developed disorders of nervous system, including nausea (2.9%), emesis (2.2%), dizziness (1.5%), disturbance of consciousness (1.5%) and headache (0.7%). Comorbidities were present in 52.2% of patients, and among them hypertension (28.5%), diabetes (14.6%) and coronary heart disease (13.1%) are three common comorbidities, followed by cerebrovascular disease (6.6%), hepatopathy (4.4%), respiratory disease (2.9%), fracture (2.2%) and nephropathy (1.6%). In these patients, the median length of hospital stays was 17.0 days (IQR 11.0–21.0) and four patients died before following-up.

# Clinical characteristics and laboratory data of COVID-19 patients with or without anemia

A total of 61 (44.5%) COVID-19 confirmed patients were diagnosed with anemia, whose hemoglobin were below 120 g/L in males, 110 g/L in females or 100 g/L in pregnant women, while 61 (55.5%) patients were not (Table 1). No significant difference in sex proportion among the anemia group and the non-anemia group ( $P= 0.725$ ). The median age of patients with anemia was 66.4 years (IQR 58.5–79.5), older than 55.9 years (IQR 49.0–65.0) of patients in the non-anemia group ( $P< 0.001$ ). Two common symptoms, fever (77.6% vs 55.7%) and cough (57.9% vs 40.9%), of COVID-19 patients are more likely presented in patients without anemia, as compared to that has anemia. There was no significant difference in other symptoms between this two groups. Analyses of four laboratory results, which were reportedly associated with the severity of COVID-19, showed that the concentrations of C reactive protein (CRP), lactate dehydrogenase (LDH), d-dimer and interleukin 6 (IL-6) in sera of patients with anemia were similar to that without anemia. However, the proportion of severe patients in the anemia group (27.9%) was distinctly higher than that in the group with no anemia (9.2%). Similarly, significantly elevated proportion of patients with critical ill was observed in the anemia group (26.2%) compared with that of the group with no anemia (5.3%). Furthermore, the mortality of patients with anemia reached 6.6%, higher than that of the overall population in the study (2.9%). Patients meeting the recovery standards when discharged were more prevalent in the group without anemia ( $P< 0.05$ ), with the proportions as high as 73.3%.

**Table 1**  
Demographic, clinical characteristics and laboratory results of COVID-19 patients with or without anemia

<b>Variable</b>	<b>Non-anemia</b>	<b>Anemia</b>	<b>P value</b>
	(n = 76)	(n = 61)	
	n (%)	n (%)	
Male	43.0 (56.6)	37.0 (60.7)	0.728
Age			
Mean (IQR)	55.9 (49.0, 65.0)	66.4 (58.5, 79.5)	< 0.001
≤ 40	15.0 (19.7)	5.0 (8.2)	
40–60	33.0 (43.4)	16.0 (26.2)	
60–80	25.0 (32.9)	40.0 (65.6)	
>80	3.0 (3.9)	12.0 (19.7)	
Fever	59.0 (77.6)	34.0 (55.7)	0.010
Cough	44.0 (57.9)	25.0 (40.9)	0.059
Fatigue	22.0 (28.9)	11.0 (18.0)	0.162
Dyspnoea	15.0 (19.7)	17.0 (27.9)	0.312
Sputum production	11.0 (14.5)	7.0 (11.5)	0.800
Chest congestion	10.0 (13.2)	11.0 (18.0)	0.480
Muscle soreness	11.0 (14.5)	4.0 (6.6)	0.175
Diarrhoea	8.0 (10.5)	2.0 (3.3)	0.185
Nausea	3.0 (3.9)	1.0 (1.6)	0.629
Dizziness	2.0 (2.6)	0.0 (0.0)	0.502
Headache	1.0 (1.3)	0.0 (0.0)	1.000
Emesis	1.0 (1.3)	2.0 (3.3)	0.585
Disturbance of consciousness	0.0 (0.0)	2.0 (3.3)	0.196
C reactive protein > 10.0 mg/L	10 of 34 (29.4)	21 of 45 (46.7)	0.163
Lactate dehydrogenase > 250.0 U/L	5 of 33 (15.2)	15 of 46 (32.6)	0.115
D-dimer > 1 µg/L	16 of 56 (28.6)	22 of 48 (45.8)	0.102
Interleukin-6 > 10 pg/mL	8 of 34 (23.5)	14 of 19 (73.7)	0.001

Variable	Non-anemia	Anemia	Pvalue
	(n = 76)	(n = 61)	
	n (%)	n (%)	
<b>Disease grade</b>			
Ordinary	65.0 (85.5)	28.0 (45.9)	0.000
Severe	7.0 (9.2)	17.0 (27.9)	0.006
Critical	4.0 (5.3)	16.0 (26.2)	0.001
Death	0.0 (0.0)	4.0 (6.6)	0.037
Healing	56.0 (73.7)	35.0 (57.4)	0.044

## Differences in COVID-19 patients with various disease conditions

We characterize the differences between patients with ordinary, severe and critical ill (Table 2). Among these patients, 67.9% (93 cases) were classified as ordinary COVID-19, while 17.5% (24 cases) and 14.6% (20 cases) were classified as severe and critical ill, respectively. There was no difference with regard to sex in the three groups. The median age of critical patients was 74.0 years (IQR 63.8–83.0), older than that of severe (66.6 years, IQR 57.0-80.8) and ordinary patients (55.9 years, IQR 49.0-65.8). The proportion of patients that had hypertension ( $P < 0.05$ ), diabetes ( $P < 0.001$ ) and cerebrovascular diseases ( $P < 0.01$ ) was significantly elevated in the critical group, as compared to that in the ordinary and severe groups. However, there were no obvious differences in other underlying diseases between these three types of patients. As of anemia, 70.8% was in the severe group, higher than the ordinary and critical groups. We also characterized the degree of anemia in the three groups. No differences of mild anemia were observed in these groups; however the proportion of patients with severe (4.3% vs 29.2% vs 50.0%) and critical anemia (0% vs 4.2% vs 5%) increased stepwise among the ordinary, severe and critical groups. Consistent with previous reports, abnormally elevated laboratory data, including CRP ( $P < 0.05$ ), LDH ( $P < 0.001$ ), d-dimer ( $P < 0.05$ ) and IL-6 ( $P < 0.001$ ), were more common in the severe and critical groups. The mortality of critical patients was as high as 20%, while it was 0% in the ordinary and severe groups in this study. 78.5% patients met recovery standards when discharged in the ordinary group, higher than 45.8% in severe and 35.0% in critical groups ( $P < 0.001$ ).

Table 2

Demographic, clinical characteristics and laboratory results of COVID-19 patients in various conditions

<b>Variable</b>	<b>Ordinary</b>	<b>Severe</b>	<b>Critical</b>	<b>P value</b>
	(n = 93)	(n = 24)	(n = 20)	
	n (%)	n (%)	n (%)	
Male	57 (61.3)	13 (54.2)	10 (50.0)	0.583
Age				
Mean (IQR)	55.9 (49.0, 65.8)	66.6 (57.0, 80.8)	74.0 (63.8, 83.0)	< 0.001
≤ 40	18.0 (19.4)	1.0 (4.2)	1.0 (5.0)	
40–60	40.0 (43.0)	8.0 (33.3)	1.0 (5.0)	
60–80	33.0 (35.5)	9.0 (37.5)	11.0 (55.0)	
> 80	2.0 (2.2)	6.0 (25.0)	7.0 (35.0)	
Hypertension	21.0 (22.6)	8.0 (33.3)	10.0 (50.0)	0.040
Diabetes	12.0 (12.9)	0.0 (0.0)	8.0 (40.0)	< 0.001
Cardiovascular disease	8.0 (8.6)	4.0 (16.7)	6.0 (30.0)	0.031
Malignant tumor	6.0 (6.5)	5.0 (20.8)	2.0 (10.0)	0.100
Cerebrovascular disease	3.0 (3.2)	1.0 (4.2)	5.0 (25.0)	0.002
Hepatopathy	3.0 (3.2)	2.0 (8.3)	1.0 (5.0)	0.546
Respiratory system disease	1.0 (1.1%)	3.0 (12.5%)	0.0 (0.0%)	0.009
Nephroma	1.0 (1.1)	0.0 (0.0)	1.0 (5.0)	0.334
Non-anemia	65.0 (69.9)	7.0 (29.2)	4.0 (20.0)	< 0.001
Anemia	28.0 (30.1)	17.0 (70.8)	6.0 (30.0)	< 0.001
C reactive protein > 10.0 mg/L	12 of 45 (26.7)	10 of 18 (55.6)	9 of 16 (56.3)	0.031
Lactate dehydrogenase > 250 U/L	3 of 44 (6.8)	8 of 18 (44.4)	10 of 17 (58.8)	< 0.001
D-dimer > 1.0 µg/L	20 of 64 (31.3)	9 of 21 (42.9)	13 of 19 (68.4)	0.014
Interleukin-6 > 10 pg/mL	8 of 35 (22.9)	5 of 7 (71.4)	9 of 11 (81.8)	< 0.001
Death	0.0 (0.0)	0.0 (0.0)	4.0 (20.0)	< 0.001
Healing	73.0 (78.5)	11.0 (45.8)	7.0 (35.0)	< 0.001

# Relationships between anemia and classification and outcomes of COVID-19

Multivariable logistic regression analyses were performed to determine the independent factors associated with the disease classification (Table 3). We firstly compared critical patients with non-critical patients that contained ordinary and severe patients, and the results showed that ages (OR: 1.054 (95% CI 1.004 to 1.106),  $P= 0.034$ ) and anemia (OR: 4.895 (95% CI 1.118 to 21.418),  $P= 0.035$ ) were two valid factors that were related to critical COVID-19 condition (Table 4). Then, ordinary patients were compared with severe and critical patients using logistic regression analyses, the results showed that ages (OR: 1.072 (95% CI 1.023 to 1.123),  $P= 0.003$ ) and anemia (OR: 8.187 (95% 2.544 to 26.343),  $P< 0.001$ ) remained be closely associated with severe and critical COVID-19 conditions (Table 4). Of note, these results demonstrate that anemic COVID-19 patients were 8.2 times more likely to develop severe or critical ill than COVID-19 patients without anemia.

Table 3

Risk factors associated with critical versus ordinary/severe and severe/critical versus ordinary disease in logistic regression analysis

Variable	Critical vs ordinary/severe			Severe/critical vs ordinary		
	OR	95% CI	P value	OR	95% CI	P value
Male	0.865	0.245 to 3.061	0.822	0.627	0.209 to 1.883	0.405
Age	1.054	1.004 to 1.106	0.034	1.072	1.023 to 1.123	0.003
Hypertension	0.654	0.172 to 2.493	0.534	0.310	0.083 to 1.162	0.082
Anemia	4.895	1.118 to 21.418	0.035	8.187	2.544 to 26.343	< 0.001
D-dimer > 1.0 µg/L	2.905	0.871 to 9.693	0.083	1.790	0.601 to 5.329	0.295
Lymphocytes < 1.1 × 10 <sup>9</sup> /L	2.692	0.788 to 9.198	0.114	1.640	0.511 to 5.269	0.406

To investigate the predictors of recovery in COVID-19 patients, we performed multivariable logistic regression analyses of the associations between the potential factors and healing of illness. Comparison of patients who were cured (meeting standards of hospital discharge) and those who were not cured showed that anemia and other factors were not associated with healing of COVID-19 during following-up (Table 4).

**Table 4**  
 Risk factors associated with the healing of COVID-19 in logistic regression analysis

Variable	OR	95% CI	P value
Male	0.313	0.086 to 1.133	0.077
Age	0.984	0.938 to 1.031	0.494
Hypertension	1.435	0.362 to 5.695	0.607
Diabetes	0.593	0.125 to 2.815	0.510
Anemia	1.062	0.203 to 5.550	0.943
C reactive protein >10.0 mg/L	0.834	0.221 to 3.143	0.789
Lactate dehydrogenase >250 U/L	1.040	0.243 to 4.459	0.958
D-dimer >1.0 µg/L	1.378	0.383 to 4.963	0.624
Lymphocytes <1.1×10 <sup>9</sup> /L	0.487	0.101 to 2.347	0.370
Lymphocytes (%) <20%	0.750	0.130 to 4.326	0.748

## Discussion

A number of COVID-19 patients with rare anemias, including aplastic anemia,<sup>16</sup> sickle cell anemia,<sup>17</sup> thalassemia,<sup>18</sup> autoimmune hemolytic anemia,<sup>19</sup> and megaloblastic anemia,<sup>20</sup> have been recently reported. However, little proportion of attention was paid on common anemia in COVID-19 patients. Our data demonstrated that approximately 44.5% of COVID-19 patients were proved to have anemia (common) and the proportions were dramatically higher than that of other underlying diseases, such as hypertension, diabetes, cardiovascular disease and malignant tumor.<sup>11, 21</sup> In this study, we firstly presented clinical characteristics and laboratory results of COVID-19 patients with anemia in a large amount (137 cases) and meanwhile investigating the impact of anemia on COVID-19.

After comparison of the symptoms between anemic COVID-19 patients and the counterparts without anemia, the results showed that anemic patients less likely to develop fever and cough in the early stage of COVID-19, indicating the concealment of COVID-19 patients with anemia. Fever has been extensively utilized as an indicator to screen suspected COVID-19 patients at public places, such as airports, mall and cinemas, and it has been proved effectively.

Therefore, the COVID-19 patients with anemia may be easily to evade the screening and brings a huge challenge to the control and management of this epidemic.

Meanwhile, COVID-19 patients with anemia are more likely to have decreased interleukin-6 (IL-6), which indicates severe inflammatory reaction.<sup>22</sup> Additionally, previous study has proved the association of

elevated serum levels of IL-6 with progress of COVID-19.<sup>11</sup> These results suggest that anemic patients possess a high possibility to develop severe pneumonia. Consistently, comparison of the severe COVID-19 patients in anemia group and non-anemia group revealed that 27.9% of the anemic patients ultimately developed severe pneumonia, significantly higher than that of patients without anemia. Moreover, the anemia was identified as an independent risk factor of the severe and critical COVID-19, as evidenced by analyses of multivariable logistic regression. The related OR value demonstrates that COVID-19 patients with anemia are more likely to develop severe pneumonia, with the possibility of 8.2 times higher than that having no anemia. Severe COVID-19 generally accompanies the low oxygen levels of arterial blood, and for instance, a vital criterion of identifying severe pneumonia was to determine whether the blood oxygen saturation was below 93% when rest. In anemia patients, the insufficient hemoglobin impaired the oxygenation capability of blood and exacerbated the anoxia in multiply organs and tissues, thus leading to aggravation of pneumonia. In addition, the enhanced inflammation reaction, as evidenced by elevated levels of IL-6, in anemic patients was speculated to be yet contributed to the progress of COVID-19.

This work firstly presents a large retrospective cohort study among COVID-19 patients with anemia and proves the association of anemia with severe pneumonia. Therefore, the thorough evaluation of anemia is recommended in COVID-19 patients when diagnosis. Timely treating anemia and increasing the hemoglobin levels are important in controlling the progress of pneumonia.

## **Limitations**

This study has several limitations. First, given that mild patients were treated in cabin hospitals but not in Wuhan Union Hospital, we fail to enroll this type of COVID-19 patients in our cohort, thereby being unable to comprehensively characterize the clinical characteristics of patients with anemia. Second, this is a single-centre study and more laboratory results, such as albumin, aspartate aminotransferase (AST), interferon- $\gamma$  (IFN- $\gamma$ ) and transforming growth factor- $\beta$  (TGF- $\beta$ ), need to be included. Third, we did not collect and analyze the therapeutic information of anemia in COVID-19 patients. These data would enhance the understanding that whether or which anemic treatments improve the severity of pneumonia. Despite of the aforementioned limitations, our study carefully described the clinical characteristics of anemic patients with ordinary, severe and critical COVID-19 and meanwhile elucidated the interaction between anemia and COVID-19.

In conclusion, COVID-19 patients having anemia are more likely to develop severe pneumonia and need timely intervention and more attentions.

## **Declarations**

## **Author Contributions**

CC and WZ contributed to data collection. CC, WZ, ZL and CZ contributed to data analysis. All authors contributed to data interpretation. CC and WZ drafted the manuscript. All authors critically commented on

the manuscript and approved the final version.

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## Competing interests

The authors declare that they have no conflicts of interest.

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