Short Communication

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Association of anemia and COVID-19 in hospitalized patients

Chong Chen[‡,1], Wenhui Zhou[‡,1], Wenliang Fan[1], Xianying Ning[1], Shuai Yang[1], Ziqiao Lei[*,1] & Chuansheng Zheng[**,1]

[1]Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science & Technology, 1277 Jiefang Ave., Wuhan, China

*Author for correspondence: Tel.: +86 278 572 6214; leiziqiaowhxh@163.com

**Author for correspondence: Tel.: +86 278 572 6214; hqzcsxh@sina.com

‡Authors contributed equally

Aim: COVID-19 is a major threat to public health worldwide. A large proportion of COVID-19 patients is proved to develop anemia. Herein, we investigate the association between anemia and severe pneumonia. **Materials & methods:** 137 of COVID-19-confirmed patients admitted to Wuhan Union Hospital (Wuhan, China) from 13 February to 17 March 2020 were included. Their clinical characteristics and laboratory data were studied, and multivariable logistic regression analyses were performed. **Results:** The anemic patients were less likely to develop fever in the early stage of COVID-19. Elevated IL-6 levels were found in anemic COVID-19 patients compared with those without anemia. COVID-19 patients with anemia had an 8.2 times greater possibility of developing severe pneumonia compared with their counterparts without anemia. **Conclusion:** This study comprehensively describes the clinical characteristics of anemic patients with ordinary, severe and critical COVID-19 and demonstrates the close relationship between the anemia and severe COVID-19.

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COVID-19 has become an extensive pandemic worldwide since its outbreak in Wuhan (Hubei Province, China), in December 2019 [1,2]. As of 26 July 2020, there are approximately 15,785,000 confirmed COVID-19 cases in 215 countries or regions around the world, with nearly half distributed in the United States, Brazil and India [3]. Dramatically increased cases of COVID-19 led to overwhelmed medical resources and brought huge challenges to global public health [4]. Up to now, COVID-19 has resulted in 3,112,041 of deaths due to the acute respiratory failure or other associated complications, and the number of deaths globally continues to increase [3].

In COVID-19-confirmed patients, pneumonia weakens lung function, which persistently provides oxygen to blood through breathing and gas exchange [5–7]. As the illness worsens, oxygen levels in blood drop, and the oxygen supply of tissues is limited [8]. In most cases, high-throughput oxygen supply via nasal tubes is performed to elevate partial pressure of arterial oxygen (PaO_2), thus alleviating hypoxia. As is well known, hemoglobin (Hb) acts as an oxygen carrier, which combines oxygen in lung tissues and releases oxygen in various organs; meanwhile, it plays a crucial role in maintaining the balance of blood oxygen and PaO_2 level [9]. Therefore, a decrease of Hb in COVID-19 patients, also known as anemia [10], is speculated to weaken the capability of oxygen delivery and to aggravate the illness. Although the understanding of COVID-19 has grown tremendously in a short period of time [11–15], the association between anemia and COVID-19 remains 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.

Material & methods

Study design

A retrospective research was conducted by using data from the electronic medical records system. In this study, we enrolled 162 COVID-19-confirmed patients who were admitted to Union Hospital, Tongj Medical College, Huazhong University of Science and Technology (Wuhan, China), from 13 February to 17 March 2020. Among these patients, 25 were excluded due to incomplete medical records (23 cases) and lack of positive reverse transcriptase (RT)-PCR results (two cases). Ultimately, 137 patients were included in this cohort.

In accordance with official treatment and management policy, all costs of COVID-19 treatment were free, and all the patients with severe or critical illness were admitted into the designated hospitals for treatment. In addition, mild cases and most ordinary cases were treated in the cabin hospitals. In this study, we enrolled three types of patients, including ordinary, severe and critical patients. COVID-19 cases were confirmed by positive RT-PCR results and ground-glass opacities in chest computed tomography (CT) scan. All cases in this study were reviewed by three physicians (C Chen, WH Zhou and ZQ Lei) under the COVID-19 diagnosis and treatment guideline issued by the National Health Committee of China (7th edition) and the WHO interim guidance.

Data collection

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

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 Hb, C-reactive protein (CRP), lactate dehydrogenase (LDH) and lymphocyte count, were also acquired from the Department of Clinical Laboratory. Hb and blood cell counts were tested using the Automatic Blood Cell Analyzer (BC5500, Mindray, China).

Definitions

Anemia in adults was defined as follows: mild – Hb levels in whole blood <120 g/l in males, 110 g/l in females or 100 g/l in pregnant women; moderate – Hb levels in whole blood ≤ 90 g/l and >60 g/l; severe – Hb levels in whole blood ≤ 60 g/l and ≥ 30 g/l; and critical – Hb levels in whole blood ≤ 30 g/l.

According to the COVID-19 diagnosis and treatment guideline, we classified the COVID-19 patients in this study with ordinary, severe and critical illness as follows: ordinary – patients developed common symptoms, including fever, cough, sore throat and so on, while having typical ground-glass opacities but no signs of severe pneumonia; severe – patients met one of the several criteria, including respiratory distress, respiratory rates ≥ 30/min, blood oxygen saturation $\leq 93\%$ at rest, or ground-glass lesions $>50\%$ within 48 h; critical – patients met one of several criteria, including respiratory failure, requiring mechanical ventilation, shock or multiple organ failure.

The patients had to meet the following requirements before being discharged from the hospital: maintaining normal temperature for more than 3 days; two consecutive negative RT-PCR results (every two sampling intervals had to be ≥ 24 h apart); obvious improvement of clinical symptoms; and significant improvement of pulmonary inflammation on CT scan.

Statistical analysis

All data were documented in Excel and analyzed using SPSS software (version 21). Continuous variables were expressed as median (interquartile range [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 sex, age, underlying disease, CRP, d-dimer, and lymphocyte count, 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 who had incomplete medical records and two inpatients without confirmed SARS-CoV-2 RT-PCR assay, we included 137 incident cases of COVID-19 who were admitted to Wuhan Union Hospital from 13 February to 17 March 17 2020. Among them, 67.9% (93 cases) were ordinary patients, 17.5% (24 cases) were severe and 14.6% (20 cases) were critically ill. The median age of the 137 COVID-19 patients was 60 years (IQR: 49.0–70.0 years; range: 20–93 years) with 58.4% being male. The most common symptoms of patients were fever (67.9%), cough (50.4%), fatigue (24.1%) and dyspnea (23.4%), followed by chest congestion (15.3%), sputum production (12.4%), muscle soreness (10.9%) and diarrhea (7.3%). A small 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 mellitus (14.6%) and coronary heart disease (13.1%) were the three commonest 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 stay was 17.0 days (IQR: 11.0–21.0 days), and four patients died before follow up. Additionally, four pregnant women were included in this study, 75% of whom (three cases) had ordinary COVID-19 without anemia and 25% (1 case) ordinary COVID-19 with mild anemia.

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

Sixty-one (44.5%) COVID-19-confirmed patients were diagnosed with anemia, with Hb <120 g/l in males, 110 g/l in females or 100 g/l in pregnant women, and 76 (55.5%) patients were not (Table 1). Further, 46.3% of male patients (37 cases) and 42.1% (24 cases) of female patients had anemia. No significant difference in sex proportion was observed among the anemic and the nonanemic groups ($p = 0.725$). The median age of patients with anemia was 66.4 years (IQR: 58.5–79.5 years), higher than 55.9 years (IQR: 49.0–65.0 years) of patients in the nonanemic group ($p < 0.001$). Among 61 anemic COVID-19 patients, 62.3% (38 cases) had mild anemia, 34.4% (21 cases) had ordinary anemia and 3.3% (2 cases) had severe anemia, respectively. The common COVID-19 symptoms of fever were more likely to be present in patients without anemia compared with those with anemia (77.6% vs 55.7%). There was no significant difference in other symptoms between these two groups. Analyses of four laboratory results that were reportedly associated with the severity of COVID-19 showed that the concentrations of CRP, LDH and d-dimer in sera of patients with anemia were similar to those without anemia, whereas IL-6 was elevated in sera of patients with anemia. However, the proportion of severe patients in the anemic group (27.9%) was distinctly higher than that in the group without anemia (9.2%). Similarly, a significantly elevated proportion of patients with critical illness was observed in the anemic group (26.2%) compared with the group without anemia (5.3%). Furthermore, mortality in patients with anemia reached 6.6%, which was higher than that of the overall study population (2.9%). Patients meeting recovery standards for discharge were more prevalent in the group without anemia ($p < 0.05$), with proportions as high as 73.3%.

Differences in COVID-19 patients with various disease conditions

We characterized the differences between patients with ordinary, severe and critical illness (Table 2). Among these patients, 67.9% (93 cases) were classified as ordinary COVID-19, and 17.5% (24 cases) and 14.6% (20 cases) were classified as severe and critical illness, respectively. For females, 63.2% (36 cases), 19.3% (11 cases) and 17.5% (10 cases) were classified as ordinary, severe and critical COVID-19, 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 years), older than that of severe (66.6 years, IQR: 57.0–80.8 years) and ordinary patients (55.9 years, IQR: 49.0–65.8 years). Age-related diseases, such as cardiovascular disease, hypertension, diabetes and dementia, might contribute to the severe pneumonia of older COVID-19 patients [16–19]. The proportion of patients who had hypertension ($p < 0.05$), diabetes ($p < 0.001$) and cerebrovascular disease ($p < 0.01$) was significantly elevated in the critical group compared with that in the ordinary and severe groups. However, there were no obvious differences in other underlying diseases between these three types of patients. As for anemia, 70.8% was in the severe group, higher than that in the ordinary and critical groups. We also characterized the degree of anemia in these 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

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

Variable	Nonanemic (n = 76), n (%)	Anemic (n = 61), n (%)	p-value
Male	43.0 (56.6)	37.0 (60.7)	0.728
Age (years)			
Mean (interquartile range)	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
Dyspnea	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
Diarrhea	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
IL-6 >10 pg/ml	8 of 34 (23.5)	14 of 19 (73.7)	0.001
Disease grade			
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

($p < 0.001$), 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%, whereas it was 0% in the ordinary and severe groups in this study. Overall, 78.5% patients met recovery standards in the ordinary group, compared with 45.8% in the severe and 35.0% in the critical group ($p < 0.001$).

Relationships between anemia & classification & outcomes of COVID-19

Multivariable logistic regression analyses were performed to determine the independent factors associated with the disease classification (Table 3). We first compared critical with noncritical patients that included ordinary and severe patients, and results showed that age (odds ratio [OR]: 1.054; 95% CI: 1.004–1.106; p = 0.034) and anemia (OR: 4.895; 95% CI: 1.118–21.418; p = 0.035) were two factors 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 age (OR: 1.072; 95% CI: 1.023–1.123; p = 0.003) and anemia (OR: 8.187; 95% CI: 2.544–26.343; $p < 0.001$) remained closely associated with severe and critical COVID-19 conditions (Table 4). Of note, these results demonstrate that anemic COVID-19 patients are 8.2 times more likely to develop severe or critical ill than COVID-19 patients without anemia.

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 the standards for hospital discharge) and those who were not cured showed that anemia and other factors were not associated with COVID-19 healing during follow up (Table 4).

Table 2. Demographic, clinical characteristics and laboratory results of COVID-19 patients in various conditions.

Variable	Ordinary (n = 93), n (%)	Severe (n = 24), n (%)	Critical (n = 20), n (%)	p-value
Male	57 (61.3)	13 (54.2)	10 (50.0)	0.583
Age (years)				
Mean (interquartile range)	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
Nonanemic	65.0 (69.9)	7.0 (29.2)	4.0 (20.0)	<0.001
Anemia	28.0 (30.1)	17.0 (70.8)	16.0 (80.0)	<0.001
Mild anemia	24.0 (25.8)	9.0 (37.5)	5.0 (25)	
Moderate anemia	4.0 (4.3)	7.0 (29.2)	10.0 (50)	
Severe anemia	0.0 (0.0)	1.0 (4.2)	1.0 (5.0)	
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
IL-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

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		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Male	0.865	0.245–3.061	0.822	0.627	0.209–1.883	0.405
Age	1.054	1.004–1.106	0.034	1.072	1.023–1.123	0.003
Hypertension	0.654	0.172–2.493	0.534	0.310	0.083–1.162	0.082
Anemia	4.895	1.118–21.418	0.035	8.187	2.544–26.343	<0.001
D-dimer >1.0 μg/l	2.905	0.871–9.693	0.083	1.790	0.601–5.329	0.295
Lymphocytes $<1.1 \times 10^9$/l	2.692	0.788–9.198	0.114	1.640	0.511–5.269	0.406

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

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

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Discussion

A number of cases of COVID-19 patients with rare anemias, including aplastic anemia [20], sickle cell anemia [21], thalassemia [22], autoimmune hemolytic anemia [23] and megaloblastic anemia [24], have been recently reported. Iron deficiency, folate deficiency, vitamin B_{12} deficiency, inflammation and hemolysis contribute to most types of anemia, which are termed common anemia. However, little attention has been paid to common anemia in COVID-19 patients. Our data demonstrate 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 [11,25]. No obvious bone marrow depression was observed in these patients. However, whether pneumonia-induced infection was a cause of anemia remained unclear, and further study was necessary to determine this. In this study, we presented clinical characteristics and laboratory results of COVID-19 patients with anemia in a large number of patients (137) and investigated the impact of anemia on COVID-19.

After comparison of the symptoms among anemic COVID-19 patients and their counterparts without anemia, the results showed that anemic patients were less likely to develop fever in the early stage of COVID-19, and thus COVID-19 was not noted early on in patients with anemia. Fever has been extensively used as an indicator to screen suspected COVID-19 patients in public places, such as airports, malls and cinemas, and it has proved to be effective. Therefore, COVID-19 patients with anemia may evade screening, which presents a significant challenge to the control and management of the epidemic.

Meanwhile, COVID-19 patients with anemia are more likely to have increased IL-6, indicating a severe inflammatory reaction [26]. Previous work has proved the association of elevated serum levels of IL-6 with the progression of COVID-19 [11]. These results suggest that anemic patients possess a high probability of developing severe pneumonia, which is consistent with a recently reported study [27]. Comparison of severe COVID-19 patients in the anemia and nonanemic groups revealed that 27.9% of the anemic patients ultimately developed severe pneumonia, which was significantly higher than patients without anemia. Moreover, anemia was identified as an independent risk factor of severe and critical COVID-19, as evidenced by multivariable logistic regression. The related OR analyses demonstrate that COVID-19 patients with anemia are more likely to develop severe pneumonia – 8.2 times more likely than their counterparts without anemia. Severe COVID-19 is generally accompanied by low oxygen levels of arterial blood, and a vital criterion for identifying severe pneumonia is to determine whether blood oxygen saturation is <93% at rest. In anemic patients, the insufficient Hb impaired the oxygenation capability of blood and exacerbated the anoxia in multiple organs and tissues, 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 contribute to the progress of COVID-19.

Conclusion

This work presents a large retrospective cohort study among COVID-19 patients with anemia and investigates the association of anemia with severe pneumonia. Anemic patients are less likely to develop fever in the early stage of COVID-19 and have elevated IL-6 levels compared with their counterparts without anemia. As evidenced by multivariable logistic regression analyses, COVID-19 patients with anemia had an 8.2 times greater possibility of developing severe pneumonia compared with COVID-19 patients without anemia. In conclusion, COVID-19 patients with anemia were more likely to develop severe pneumonia and need timely intervention and more attention.

Limitations

This study has several limitations. First, given that mild patients were treated in cabin hospitals but not in Wuhan Union Hospital, we failed to enroll this type of COVID-19 patient in our cohort. We are therefore unable to comprehensively characterize the clinical characteristics of patients with anemia. Second, this was a single-center study, and more laboratory results, such as albumin, aspartate aminotransferase, IFN-γ and TGF-β, should be included. Third, we did not collect and analyze the therapeutic information of anemia in COVID-19 patients. These data would enhance the understanding whether or which anemic treatments improved the severity of pneumonia. Fourth, because this was a retrospective study, we were unable to accurately manipulate exposure factors, covariates and potential confounders. Despite the aforementioned limitations, our study carefully described the clinical characteristics of anemic patients with ordinary, severe and critical COVID-19 and also elucidated the interaction between anemia and COVID-19.

Summary points

- Anemic patients are less likely to develop fever in the early stage of COVID-19, which may conceal the presence of COVID-19 in patients with anemia.
- COVID-19 patients with anemia have elevated IL-6 compared with their counterparts without anemia, which suggests severe inflammatory reaction.
- As evidenced by multivariable logistic regression analyses, COVID-19 patients with anemia are 8.2 times more likely to develop severe pneumonia compared with their counterparts without anemia.
- Anemia is closely associated with severe COVID-19, and anemic COVID-19 patients need timely intervention and more attention.

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Availability of data and materials

All data and materials can be acquired from the corresponding author.

Ethical conduct of research

This study was approved by the Wuhan Union Hospital of Huazhong University of Science and Technology Institutional Review Board and informed consent were waived.

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