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Use of low molecular weight heparin and hemoglobin fall in COVID-19 patients

A STROBE-compliant study

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Abstract

In patients with coronavirus disease 2019 (COVID-19), anticoagulation was suggested as a mitigating strategy. However, little research has been conducted on the adverse consequences of anticoagulant medication. This study aimed to investigate the adverse effect of low molecular weight heparin (LMWH) on hemoglobin fall in COVID-19 treatment. The electronic medical records of COVID-19 patients with pneumonia were collected (including clinical characteristics, vaccination status, complete blood count, coagulation profile, inflammatory cytokines, serum biochemical indicators, and computerized tomography imaging score). Whether they received LMWH, patients were divided into the LMWH group and the control group. Count data were represented as frequency distribution, and a 2-tailed test was used to compare the 2 groups. Spearman rank correlation was used to evaluate the interrelation between changes in hemoglobin and LMWH. The confounding factors were excluded by logistic regression analysis. A total of 179 COVID-19 pneumonia patients were enrolled (81 in the LMWH group and 98 in the control group). The change in hemoglobin was −6.0g/L (IQR −10.8 to 1.0) in the LMWH group and −2.0g/L (IQR −7.0 to 4.0) in the control group ($P < .001$, between-group difference, −5.0 g/L; 95% confidence interval, −7.0 to −3.0, calculated with the use of the Mann–Whitney *U* test and the Hodges–Lehmann estimate of confidence intervals for pseudo-medians). The results of multivariate regression analysis showed that after adjusting for confounding factors, LMWH use was not associated with a decrease in hemoglobin ($P > .05$). In nonsevere COVID-19 patients with pneumonia, the preventive use of LMWH did not lower hemoglobin.

Abbreviations: COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, CT imaging score = computerized tomography imaging score, IgG = immunoglobulin G, IgM = immunoglobulin M, LMWH = low molecular weight heparin, RT-PCR = reverse transcription-polymerase chain reaction.

Keywords: adverse effect, anticoagulation, COVID-19, hemoglobin, low molecular weight heparin

1. Introduction

The World Health Organization (WHO) proclaimed coronavirus disease 2019 (COVID-19) a worldwide pandemic on March 11, 2020. As of March 29, 2022, WHO had received reports of 481,756,671 confirmed cases of COVID-19, with 6127,981 deaths.[1] Inflammation and thrombosis are linked to COVID-19.[2–5] Postmortem examinations of patients with COVID-19 revealed thrombosis in minor pulmonary vessels and extrapulmonary organs with no evidence of coronavirus penetration.[6] Both thrombotic and hemorrhagic pathologies should be taken into account in COVID-19.[7] In patients with COVID-19, anticoagulation was suggested as a mitigating strategy.[8–10] Low molecular weight heparin (LMWH) produces a significant anticoagulant effect by activating antithrombin and may increase the risk of bleeding events.[11]

Using LMWH as an initial anticoagulant has been proven to lower mortality by preventing the formation of microthrombi and pulmonary coagulopathy.[12] In critically ill COVID-19 patients, anticoagulant medication with LMWH reduced the incidence of thrombotic complications.[13,14] Compared to usual-care thromboprophylaxis, an early approach of therapeutic-dose anticoagulation with LMWH enhanced the likelihood of survival to hospital discharge with less cardiovascular or respiratory organ support in noncritically ill patients with COVID-19.[15] Nonetheless, little research has examined LMWH adverse consequences, such as anemia.

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A considerable hemoglobin loss without overt bleeding is possible during the early postanticoagulation phase, unlike serious bleeding complications.[16] Compared to preanticoagulation levels, postanticoagulation hemoglobin can help gauge the blood loss from anticoagulants.

Our study aimed to investigate the adverse effect of hemoglobin fall of LMWH on the adjuvant treatment of COVID-19 patients with pneumonia through retrospective analysis.

2. Methods

2.1. Study design

We carried out a noninterventional, retrospective cohort study of patients with COVID-19 from the COVID-19 designated hospital in Xiamen, China. We abide by and cite the STROBE guidelines for reporting our observational study.

2.2. Research subjects

A retrospective cohort research was done to assess the therapeutic efficacy of LMWH on COVID-19. The COVID-19 designated hospital in Xiamen, China for patients with COVID-19, was the site of all cases in this investigation. This study was approved by the hospital institutional review board. We retrospectively collected the electronic medical records of 179 COVID-19 patients with pneumonia who were admitted between September 11, 2021, and October 15, 2021 (Figure 1 shows the case inclusion flowchart), of whom 81 received LMWH treatment (manufacturer: ALFASIGMA, 4250 IU/daily subcutaneously) for 5 days (defined as the LMWH group) and 98 without LMWH treatment (defined as the control group) during their hospitalization. The criteria for using LMWH have elevated D-dimer or the presence of risk factors for hypercoagulability.[8]

As a designated hospital for treating patients with COVID-19, our hospital received 241 patients from September 11, 2021, to October 15, 2021. Case screening was performed after all patients were discharged from the hospital. According to the Diagnosis and Treatment Plan of COVID-19 suggested by the National Health Commission of China, the severity of the disease was classified.[8] Briefly, the mild disease had a diagnosis of COVID-19, but with no hypoxia or evidence of viral pneumonia; the moderate disease had clinical signs of pneumonia but had an oxygen saturation >90% on room air; the severe disease had signs of pneumonia with tachypnea >30 breaths per minute, severe respiratory distress or an oxygen saturation <90% on room air; and critical disease had acute respiratory distress syndrome, sepsis, or septic shock. Patients with moderate disease, namely, patients with pneumonia but not severe, were included in the study. 54 mild patients and 8 severe patients (diagnosed according to the New Coronavirus Pneumonia Diagnosis Program (8th edition) published by the National Health Commission of China)[8] were excluded. Of the 179 moderate patients, 81 received LMWH (LMWH group), and 98 patients were not treated with LMWH (control group).

The diagnosis of COVID-19 was according to the New Coronavirus Pneumonia Diagnosis Program (8th edition)[8] and confirmed by RNA detection of the SARS-CoV-2 in a clinical laboratory of the COVID-19 designated hospital in Xiamen, China. According to the Diagnosis and Treatment Plan of COVID-19 suggested by the National Health Commission of China, the severity of the disease was classified.[8]

2.3. Data collection

The electronic medical record was used to extract clinical data. The clinical characteristics, vaccination status, complete blood count, coagulation profile, inflammatory cytokines, and serum biochemical indicators (including liver function, kidney function, lactate dehydrogenase, C-reactive protein (CRP), and electrolytes), RT-PCR cycle threshold, IgM, IgG, CT imaging score (namely CT visual and quantitative evaluation was based on summing up the acute lung inflammatory lesions involving each lobe, which was scored as 0 (0%), 1 (1–25%), 2 (26–50%), 3 (51–75%), or 4 (76–100%), respectively)[17] of 179 patients with COVID-19 were retrospectively analyzed. Two researchers also independently reviewed the data collection forms to double-check the data collected.

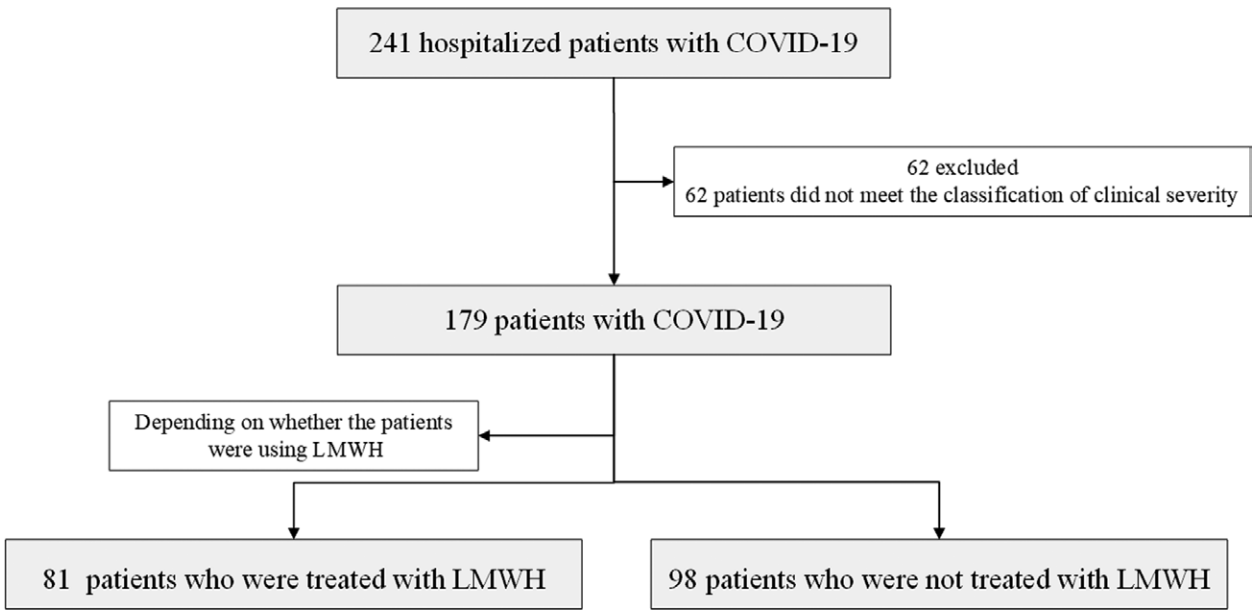

Figure 1. Flow chart for the inclusion and exclusion of patients with coronavirus disease 2019 (COVID-19). Based on strict inclusion and exclusion criteria, 179 patients with COVID-19 pneumonia treated at the hospital between September 11, 2021, and October 15, 2021, were selected for the study, of which 81 underwent low molecular weight heparin (LMWH) treatment (LMWH group), and 98 did not (control group) during hospitalization.

2.4. Statistical analysis

Data were analyzed using SPSS 26.0 for Windows (SPSS Inc). The picture was made by GraphPad Prism 8 for Windows (GraphPad Inc). The sensitivity analysis was calculated by G*Power 3.1 for Windows. The measurement data were presented as mean ± SD in normal distribution and median ± quartile in nonnormal distribution. If the distributions of the 2 groups are normal and the variance is uniform, the unpaired 2-sided Student t-test is used. The nonparametric test is employed when the distributions of the 2 groups are nonnormal or the variance is not uniform. Count data were represented as frequency distribution, and a 2-tailed test was used to compare the 2 groups. Changes in laboratory findings = after treatment value - before treatment value. In the comparison of hemoglobin changes between the LMWH group and the control group, results of sensitive analysis: input parameters: α err prob = 0.05, Power(1- β err prob) = 0.8, LMWH group = 81, Control group = 98; output parameters: noncentrality parameter δ = 2.82, Critical t = 1.97, Df = 168.93, effect size d = 0.43. Spearman rank correlation was used to evaluate the interrelation between changes in hemoglobin and LMWH. The confounding factors were excluded by binomial logistic regression analysis. The hemoglobin changes were used as the dependent variable, LMWH used or not, and other significant factors in nonparametric tests were used as independent variables. $P < .05$ was judged statistically significant.

3. Results

3.1. General characteristics of COVID-19 patients with pneumonia between groups based on LMWH usage

All individuals with moderate illness were evaluated to ensure their severity did not affect the research outcomes. As shown in Table 1, the LMWH group consisted of 36 men and 45 women aged between 34.0 and 51.0 years (median age = 43.0 years), and the control group consisted of 46 men and 52 women aged between 30.0 and 45.0 years (median age = 39.0 years). There were no significant differences in sex, comorbidity, onset symptoms (cough, dyspnea, sputum, pharyngalgia, pharyngoxerosis, sniffle, and myalgia), pulse, respiratory rate, systolic pressure, diastolic pressure, a saturation of pulse oxygen on exertion, therapy (Chinese traditional medicine, prone position, and glucocorticoid) and vaccination status between the 2 groups. There were significant differences in age, BMI, onset symptoms (fever, fatigue), temperature, a saturation of pulse oxygen at rest, therapy (thymosin α1 and glucocorticoid), CT imaging score, length of temperature drop, and hospital length of stay between the 2 groups (all $P < .05$).

3.2. Influence of LMWH on changes in hemoglobin in COVID-19 patients with pneumonia

As shown in Table 1, in COVID-19 patients with pneumonia, there were no significant differences in the enumeration of leukocyte, neutrophil count, lymphocyte count, platelet, prothrombin time, C-reaction protein, D-dimer, creatine kinase, creatine kinase MB, total bilirubin, total bilirubin, lactic dehydrogenase, interleukin-6 and procalcitonin between the 2 groups before and after LMWH treatment. As shown in Figure 2, the changes in hemoglobin were −6.0 (IQR −10.8 to 1.0) in the LMWH group and −2.0 (IQR −7.0 to 4.0) in the control group ($P < .001$, between-group difference, −5.0 g/L; 95% confidence interval, −7.0 to −3.0, calculated with the use of the Mann–Whitney U test and the Hodges–Lehmann estimate of confidence intervals for pseudo-medians). For the Mann-Whitney test, the effect size is given by the rank biserial correlation. Rank-Biserial Correlation = 0.329, 95% CI for Rank-Biserial Correlation = [0.190, 0.456].

As shown in Table 2, LMWH was significantly correlated with the changes in hemoglobin ($P < .001$, $R = 0.268$).

As shown in Table 3, there were statistically significant differences in diabetes, fever, pulse, glucocorticoid use, LMWH use, CT imaging score, and fibrinogen between the changes in hemoglobin < -8g/L group and the changes in hemoglobin ≥ -8g/L group ($P < .05$).

As shown in Table 4, hemoglobin decline was defined as a change in hemoglobin of <25 percent of a total patient (-8g/L). Hemoglobin decline was used as the dependent variable, and the potential influencing factors in 1-way ANOVA tests were used as independent variables. The results of multivariate regression analysis showed that after adjusting for confounding factors (fever, diabetes, pulse, use of glucocorticoid, CT imaging score, and fibrinogen), LMWH use was not associated with a decrease in hemoglobin ($P > .05$).

4. Discussion

This article examined the adverse effects of LMWH in COVID-19 patients with pneumonia through a retrospective study. We found that in COVID-19 patients with pneumonia, a prophylactic dose of LMWH was significantly correlated with the changes in hemoglobin. After adjusting for confounding factors, a prophylactic dose of LMWH use was not associated with a decrease in hemoglobin.

Heparin can prevent thrombotic problems, including systemic administration, catheter instillation, extracorporeal circuits, and coating medical devices with an artificial surface.[18] Heparin cannot lyse preexisting thrombi mechanically because it lacks intrinsic fibrinolytic action. The primary mechanism by which it acts as an anticoagulant is due to the active pentasaccharide sequence required for binding to AT-III.[19] Anticoagulation was recommended as a mitigating option because of the increased risk of macrovascular and microvascular thrombosis in individuals with COVID-19.[20,21]

Heparins, particularly LMWH, are preferred in hospitalized patients. LMWH is accessible and exposes healthcare personnel to COVID-19 patients less invasively.[20] Numerous undesirable consequences of heparin treatment are associated with heparin broad biological activity, providing significant concerns.[22] Bleeding is the primary safety risk associated with heparin usage.[9,23] Mattioli, Benfaremo[24] showed that major bleeding events occurred in 1.9 percent of elderly patients treated with COVID-19 at moderate doses of LMWH.

Several studies show that anticoagulant therapy does not increase the risk of bleeding.[25] Rentsch, Beckman[26] found that prophylactic anticoagulation compared with no anticoagulation was associated not with increasing severe bleeding.

Furthermore, the administration of a higher-dose prophylactic anticoagulation regimen than conventional doses was not linked with increased bleeding in a trial of 538 COVID-19 patients from 8 ICUs in France.[27] This study, like the previous ones, explored the side effects of LMWH in patients with COVID-19. However, no study has investigated the adverse reactions of LMWH in patients with COVID-19 using the method of hemoglobin quantification. Adverse reactions to LMWH were monitored by measuring hemoglobin levels before and after using LMWH.

At the beginning of this study, hemoglobin decreased significantly in the LMWH group than in the control group. Spearman correlation analysis suggested that the hemoglobin decrease was weakly correlated with using LMWH. Finally, the confounding factors were eliminated by binary logistic regression analysis. In nonsevere COVID-19 patients with pneumonia, our study discovered that the administration of LMWH did not lower

Table 1

Clinical characteristics of COVID-19 patients with pneumonia between groups based on LMWH.

Characteristics	LMWH group (n = 81)	Control (n = 98)	χ^2/Z value	*P* value
Age, years	43.0 (34.0–51.0)	39.0 (30.0–45.0)	–3.440	0.001
Sex			0.111	0.739
Female	45 (55.6%)	52 (53.1%)		
Male	36 (44.4%)	46 (46.9%)		
BMI (kg/m^2)	23.8 (21.6–26.5)	22.0 (19.7–24.4)	–3.237	0.001
Comorbidity				
Hypertension	8(9.9%)	9 (9.2%)	0.025	0.875
Diabetes	4 (4.9%)	4 (4.1%)	0.076	0.782
Cardiovascular disease	1 (1.2%)	0	NA	0.453
Chronic obstructive pulmonary disease	0	0	NA	NA
Malignant tumor	1 (1.2%)	0	NA	0.453
Hypoalbuminemia	1 (1.2%)	0	NA	0.453
Symptoms				
Fever (temperature ≥37.3°C)	51 (63.0%)	31 (31.6%)	17.535	0.000
Cough	45 (55.6%)	49 (50.0%)	0.549	0.459
Fatigue	21 (25.9%)	10 (10.2%)	7.655	0.006
Dyspnea	7 (8.6%)	2 (2.0%)	2.782	0.095
Sputum	16 (19.8%)	15 (15.3%)	0.612	0.434
Pharyngalgia	14 (17.3%)	26 (26.5%)	2.532	0.112
Pharyngoxerosis	19 (23.4%)	27 (27.6%)	0.389	0.533
Sniffle	8(9.9%)	10 (10.2%)	0.005	0.942
Myalgia	15 (18.5%)	10 (10.2%)	2.551	0.110
Signs				
Temperature	36.9 (36.6–37.5)	36.6 (36.3–37.1)	–2.146	0.032
Pulse	95.0 (80.0–104.0)	93.0 (82.0–99.5)	–1.428	0.153
Respiratory rate	20.0 (20.0–20.0)	20.0 (20.0–20.0)	–0.832	0.406
Systolic pressure	127.0 (113.0–133.0)	118.0 (106.0–134.0)	–1.523	0.128
Diastolic pressure	85.0 (76.0–92.0)	85.0 (77.5–95.0)	–0.062	0.950
Saturation of pulse oxygen at rest	98.0 (97.0–98.0)	98.0 (98.0–99.0)	–2.511	0.012
Saturation of pulse oxygen on exertion	97.0 (96.0–98.0)	98.0 (97.0–98.0)	–1.185	0.236
Therapy				
Chinese traditional medicine	81 (100.0%)	98 (100.0%)	NA	–
Prone position	81 (100.0%)	95 (96.9%)	1.006	0.316
Thymosin α1	11 (13.6%)	4 (4.1%)	5.211	0.022
Neutralizing antibody	16 (19.8%)	4 (4.1%)	10.974	0.001
Glucocorticoid	4 (4.9%)	0	2.948	0.086
CT imaging score	10.0 (6.0–16.0)	6.0 (3.5–10.0)	–3.623	0.000
Vaccination status			1.364	0.243
Vaccinated	74 (91.3%)	84 (85.7%)		
Unvaccinated	7 (8.6%)	14 (14.3%)		
Hospital length of stay, days	20.0 (15.0–23.0)	15.0 (13.0–22.5)	–3.627	0.000
ORF1ab	23.5 (21.1–27.7)	23.0 (20.3–27.0)	–0.289	0.772
N gene	21.3 (18.3–25.3)	21.4 (17.7–26.7)	–0.880	0.379
ORF1ab (reexamination)	29.9 (27.2–33.7)	29.8 (27.4–32.4)	–0.536	0.592
N gene (reexamination)	27.2 (24.0–32.2)	28.0 (24.0–30.4)	–0.341	0.733
ORF1ab (variation)	–5.9 (–10.7–1.0)	–6.3 (–10.6–0.14)	–0.235	0.815
N gene (variation)	–5.5 (–11.5–1.0)	–6.4 (–9.6–0.4)	–0.271	0.786
*Numeration of leukocyte, ×10^9/L	5.0 (4.3–6.7)	5.3 (4.3–6.7)	–0.778	0.436
*Neutrophil count, ×10^9/L	3.2 (2.5–4.5)	3.3 (2.3–4.3)	0.210	0.834
*Lymphocyte count, ×10^9/L	1.3 (0.9–1.3)	1.4 (1.1–1.9)	–3.240	0.001
*Hemoglobin, g/L	132.0 (122.5–146.5)	136.0 (127.3–153.8)	–1.260	0.208
*Platelet, ×10^9/L	205.0 (165.0–219.0)	202.5 (165.8–235.8)	–2.036	0.042
*Prothrombin time, s	11.4 (11.0–11.9)	11.3 (11.0–11.7)	0.054	0.957
*Activated partial thromboplastin time, s	30.8 (28.8–34.0)	32.1 (29.7–33.8)	0.609	0.543
*Thrombin time, s	16.4 (15.7–17.0)	16.4 (15.9–17.1)	–0.244	0.808
*Fibrinogen, g/L	3.9 (3.2–4.3)	3.6 (3.2–4.2)	1.482	0.138
*D - dimer, μg/mL	0.4 (0.3–0.8)	0.3 (0.2–0.4)	3.744	0.000
*C-reaction protein, mg/L	10.4 (2.9–20.3)	4.3 (1.6–8.0)	3.804	0.000
*Creatine kinase, U/L	85.0 (65.0–133.5)	82.5 (61.5–105.8)	1.310	0.190
*Creatine kinase MB, U/L	9.0 (5.5–12.5)	9.5 (5.0–13.0)	–0.266	0.790
*Total bilirubin, μmol/L	13.2 (11.0–18.9)	13.3 (11.1–18.8)	–0.088	0.930

(Continued)

Table 1

(Continued)

Characteristics	LMWH group (n = 81)	Control (n = 98)	χ^2/Z value	*P* value
*Serum albumin, g/L	40.0 (39.0–43.0)	42.0 (40.0–44.0)	–3.258	0.001
*Alanine aminotransferase, U/L	25.0 (20.0–36.5)	19.0 (16.0–27.8)	3.095	0.002
*Aspartate aminotransferase, U/L	24.0 (22.0–28.5)	21.0 (19.0–26.0)	2.819	0.005
*Creatinine, μmol/L	69.0 (56.0–81.5)	69.5 (57.3–82.5)	1.726	0.084
*Lactic dehydrogenase, U/L	163.0 (145.5–184.0)	153.0 (140.0–174.5)	1.761	0.078
*IgM, g/L	0.2 (0.1–0.3)	0.2 (0.1–0.4)	–0.126	0.900
*IgG, g/L	16.1 (5.3–36.3)	16.1 (6.2–40.5)	–1.523	0.128
*Interleukin-6, pg/mL	5.3 (1.5–12.5)	1.9 (1.5–5.7)	3.069	0.002
*Procalcitonin, ng/ml	0.1 (0.1–0.1)	0.1 (0.1–0.1)	–1.584	0.113
†Numeration of leukocyte, ×109/L	5.4 (4.3–6.6)	6.3 (5.1–7.4)	–2.817	0.005
†Neutrophil count, ×109/L	3.1 (2.4–3.9)	3.3 (2.6–4.4)	–1.665	0.096
†Lymphocyte count, ×109/L	1.7 (1.4–2.1)	2.1 (1.7–2.5)	–3.489	0.000
†Hemoglobin, g/L	129.0 (120.0–141.0)	133.5 (125.8–151.3)	–2.838	0.005
†Platelet, ×109/L	251.0 (194.0–333.0)	249.0 (196.0–310.3)	0.381	0.703
†Prothrombin time, s	11.2 (10.7–11.5)	11.4 (10.6–11.7)	–1.003	0.316
†Activated partial thromboplastin time, s	31.0 (28.0–33.6)	31.4 (29.1–34.1)	–0.995	0.320
†Thrombin time, s	16.2 (15.7–16.9)	16.7 (16.0–17.3)	–1.848	0.065
†Fibrinogen, g/L	4.4 (3.5–5.1)	3.8 (2.8–4.4)	3.881	0.000
†D - dimer, μg/mL	0.4 (0.3–0.6)	0.3 (0.2–0.4)	4.395	0.000
†C-reaction protein, mg/L	5.1 (1.7–11.0)	1.5 (0.4–3.6)	4.287	0.000
†Creatine kinase, U/L	58.0 (43.0–99.0)	62.0 (50.8–81.8)	–0.665	0.506
†Creatine kinase MB, U/L	9.0 (6.0–13.0)	8.0 (5.0–12.0)	1.109	0.268
†Total bilirubin, μmol/L	12.0 (10.7–15.6)	12.8 (9.8–15.9)	–0.662	0.508
†Serum albumin, g/L	36.0 (35.0–41.0)	41.0 (39.0–43.0)	–5.603	0.000
†Alanine aminotransferase, U/L	42.0 (25.0–74.0)	22.5 (18.0–36.3)	5.061	0.000
†Aspartate aminotransferase, U/L	33.0 (24.0–56.0)	22.0 (19.0–28.3)	5.518	0.000
†Creatinine, μmol/L	70.0 (55.0–80.0)	70.0 (55.0–84.3)	0.293	0.769
†Lactic dehydrogenase, U/L	182.0 (155.0–218.0)	162.0 (141.5–179.5)	3.561	0.000
†IgM, g/L	10.8 (3.6–19.9)	4.4 (1.1–10.7)	3.784	0.000
†IgG, g/L	419.3 (287.0–459.6)	319.3 (87.3–437.2)	3.569	0.000
†Interleukin-6, pg/mL	1.5 (1.5–5.6)	1.5 (1.5–1.5)	2.541	0.011
	0.1 (0.1–0.1)	0.1 (0.1–0.1)	1.200	0.230
‡Numeration of leukocyte, $\times10^9$/L	0.2 (-1.1–1.4)	0.5 (-0.4–1.8)	–1.539	0.124
‡Neutrophil count, $\times10^9$/L	-0.2 (-1.3–0.9)	0.2 (-0.9–1.0)	–1.244	0.214
‡Lymphocyte count, $\times10^9$/L	0.5 (0.7–0.9)	0.6 (0.2–0.8)	–0.502	0.616
‡Hemoglobin, g/L	–6.0 (–10.8--1.0)	–2.0 (–7.0–4.0)	–3.778	0.000
‡Platelet, $\times10^9$/L	55.5 (8.3–145.5)	38.0 (2.0–80.5)	–1.729	0.084
‡Prothrombin time, s	–0.3 (–0.8–0.2)	0 (–0.8–0.4)	–1.283	0.199
‡Activated partial thromboplastin time, s	–2.0 (–4.5–1.2)	–0.3 (–1.7–1.3)	–2.532	0.011
‡Thrombin time, s	–0.1 (–1.0–0.8)	–0.3 (–0.8–1.2)	–0.393	0.694
‡Fibrinogen, g/L	0.5 (–0.1–1.6)	0.1 (–0.5–0.8)	–3.014	0.003
‡D - dimer, μg/mL	0 (–0.2–0.1)	0 (-0.1–0.1)	–0.738	0.304
‡C-reaction protein, mg/L	–3.1 (–7.8–1.7)	–1.4 (-4.5–0.6)	–1.028	0.461
‡Creatine kinase, U/L	–27.0 (–55.0–8.5)	–17.0 (–38.0–0)	–2.215	0.027
‡Creatine kinase MB, U/L	0.5 (–4.8–5.0)	–2.0 (–6.5–3.0)	–0.044	0.965
‡Total bilirubin, μmol/L	–0.5 (–3.2–2.0)	-0.4 (–3.8–2.3)	–0.044	0.965
‡Serum albumin, g/L	–3.0 (–6.0--1.0)	–2.0 (–4.0–1.0)	–3.296	0.001
‡Alanine aminotransferase, U/L	10.0 (0–37.0)	2.0 (–1.0–8.0)	–3.639	0.000
‡Aspartate aminotransferase, U/L	5.0 (0–24.8)	0 (–2.5–4.0)	–4.493	0.000
‡Creatinine, μmol/L	–5.0 (–11.0–1.8)	0 (–5.0–5.0)	–3.587	0.000
‡Lactic dehydrogenase, U/L	6.0 (–14.5–41.0)	–3.0 (–16.5–22.5)	–1.959	0.050
‡IgM, g/L	10.3 (2.8–18.9)	3.1 (0.9–9.8)	–3.704	0.000
‡IgG, g/L	408.4 (235.5–447.8)	292.1 (0.7–407.4)	–3.604	0.000
‡Interleukin-6, pg/mL	–1.4 (–8.4–0)	0 (–2.6–0)	–1.616	0.106
‡Procalcitonin, ng/ml	0 (0–0)	0 (0–0)	–1.924	0.054

Data are the median (IQR) or n (%). *P* values comparing the LMWH group and control group are from the χ 2 test or nonparametric test. All laboratory findings were compared before and after treatment.
COVID-19 = coronavirus disease 2019, LMWH = low molecular weight heparin, NA = not applicable.

*Laboratory findings = value before treatment.

†Laboratory findings = value after treatment.

‡Laboratory findings = after treatment value – before treatment value.

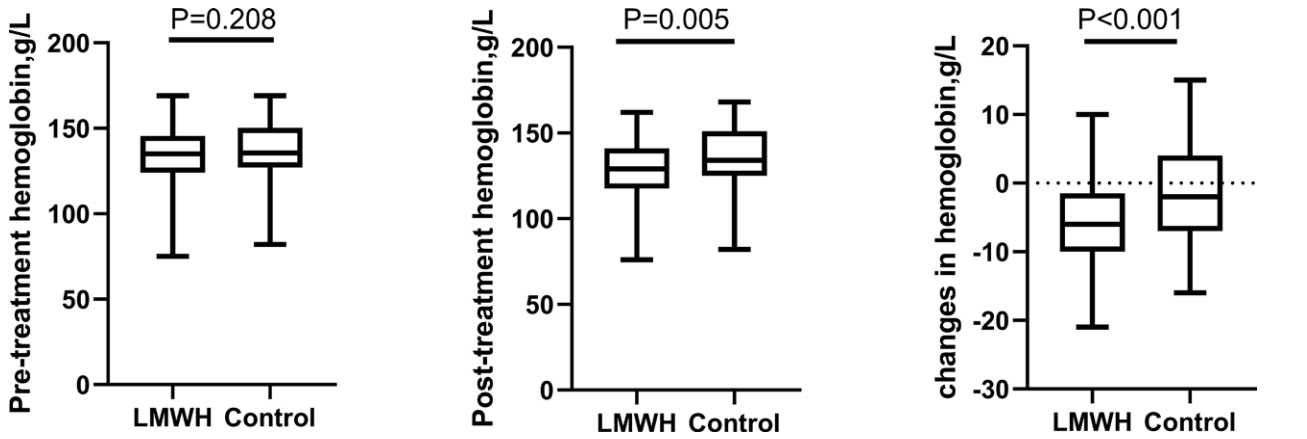

Figure 2. Comparisons of the pretreatment and posttreatment hemoglobin and changes in hemoglobin between LMWH group and control group. P values comparing hemoglobin are from the nonparametric test. LMWH, low molecular weight heparin. Nonparametric tests of pretreatment hemoglobin between LMWH and control groups showed a Z-value of −1.260 and a *P*-value of 0.208. Nonparametric tests of posttreatment hemoglobin between LMWH and control groups showed a Z-value of −2.838 and a *P*-value of 0.005. Nonparametric tests of changes in hemoglobin between LMWH and control groups showed a Z-value of −3.778 and a *P*-value of <0.001.

Table 2

Spearman rank correlation coefficients between changes in hemoglobin and general characteristics (n = 179).

Characteristics	r	*P* value
Age	−0.090	0.237
Sex	0.014	0.852
BMI	−0.217	0.004
Comorbidity		
Hypertension	0.052	0.489
Diabetes	−0.211	0.005
Cardiovascular disease	−0.115	0.130
Chronic obstructive pulmonary disease	NA	NA
Malignant tumor	0.098	0.194
Hypoalbuminemia	0.063	0.404
Symptoms		
Fever (temperature ≥37.3°C)	−0.312	0.000
Cough	−0.115	0.130
Fatigue	−0.024	0.748
Dyspnea	−0.009	0.901
Sputum	−0.099	0.190
Pharyngalgia	0.088	0.247
Pharyngoxerosis	0.001	0.992
Sniffle	0.035	0.644
Myalgia	−0.009	0.909
Signs		
Temperature	−0.195	0.010
Pulse	−0.235	0.002
Respiratory rate	−0.088	0.248
Systolic pressure	−0.065	0.394
Diastolic pressure	−0.165	0.029
Saturation of pulse oxygen at rest	−0.035	0.643
Saturation of pulse oxygen on exertion	0.014	0.852
Therapy		
LMWH	0.286	0.000
Chinese traditional medicine	NA	NA
Prone position	−0.127	0.094
Thymosin α1	−0.236	0.002
Neutralizing antibody	−0.103	0.173
Glucocorticoid	−0.172	0.022
CT imaging score	−0.269	0.000
Vaccination status	−0.127	0.094
Prothrombin time	0.067	0.375
Activated partial thromboplastin time	−0.138	0.069
Thrombin time	0.160	0.034
Fibrinogen	−0.332	0.000
D - dimer	−0.036	0.638

LMWH = low molecular weight heparin.

Table 3

Potential factors associated with hemoglobin change.

Characteristics	changes in hemoglobin < –8g/L group (n = 43)	changes in hemoglobin ≥ –8g/L group (n = 136)	χ^2/Z value	*P* value
Age, years	39.0 (34.0–48.0)	44.0 (36.3–49.0)	–0.184	0.854
Sex			0.209	0.648
Female	22 (51.2%)	75 (55.1%)		
Male	21 (48.8%)	61 (44.9%)		
BMI (kg/m^2)	23.8 (21.9–26.2)	23.0 (21.3–24.4)	1.485	0.137
Comorbidity				
Hypertension	3 (7.0%)	14 (10.3%)	0.121	0.728
Diabetes	6 (14.0%)	2 (1.5%)	9.179	0.002
Cardiovascular disease	1 (2.3%)	0	NA	0.240*
Chronic obstructive pulmonary disease	0	0	NA	NA
Malignant tumor	0	1 (0.7%)	NA	1.000*
Hypoalbuminemia	0	1 (0.7%)	NA	1.000*
Symptoms				
Fever (temperature ≥ 37.3°C)	28 (65.1%)	54 (39.7%)	8.498	0.004
Cough	24 (55.8%)	70 (51.5%)	0.247	0.619
Fatigue	7 (16.3%)	24 (17.6%)	0.043	0.836
Dyspnea	1 (2.3%)	8 (5.9%)	0.281	0.596
Sputum	9 (20.9%)	22 (16.2%)	0.516	0.473
Pharyngalgia	8 (18.6%)	32 (23.5%)	0.457	0.499
Pharyngoxerosis	14 (32.6%)	32 (23.5%)	1.395	0.238
Sniffle	2 (4.7%)	16 (11.8%)	1.126	0.289
Myalgia	5 (11.6%)	20 (14.7%)	0.258	0.612
Signs				
Temperature	36.8 (36.5–37.6)	36.7 (36.3–37.2)	1.678	0.093
Pulse	96.0 (86.0–105.0)	88.5 (78.0–98.8)	2.017	0.044
Respiratory rate	20.0 (20.0–20.0)	20.0 (20.0–20.0)	1.411	0.158
Systolic pressure	122.0 (113.0–132.0)	123.5 (111.0–138.3)	-0.138	0.890
Diastolic pressure	85.0 (74.0–92.0)	82.5 (78.0–91.8)	0.830	0.407
Saturation of pulse oxygen at rest	98.0 (97.0–99.0)	98.0 (98.0–99.0)	0.977	0.329
Saturation of pulse oxygen on exertion	97.0 (96.0–98.0)	98.0 (97.0–98.0)	-0.568	0.570
Therapy				
Chinese traditional medicine	43 (100%)	136 (100%)	NA	NA
Prone position	43 (100%)	133 (97.8%)	0.000	1.000
Thymosin α1	7 (16.3%)	8 (5.9%)	3.345	0.067
Neutralizing antibody	6 (14.0%)	14 (10.3%)	0.149	0.699
Glucocorticoid	3 (7.0%)	1 (0.7%)	NA	0.044*
LMWH	26 (60.5%)	55 (40.4%)	5.287	0.021
CT imaging score	9.0 (6.0–10.8)	11.0 (6.0–15.0)	2.478	0.013
Vaccination status			1.236	0.266
Vaccinated	40 (93.0%)	118 (86.8%)		
Unvaccinated	3 (7.0%)	18 (13.2%)		
Hospital length of stay, days	15.0 (12.0–25.0)	15.5 (13.3–23.5)	0.649	0.516
Platelet, ×109/L	182.0 (146.0–216.0)	203.0 (166.0–231.8)	–1.180	0.238
Prothrombin time, s	11.3 (11.0–11.6)	11.4 (11.0–11.8)	–0.164	0.870
Activated partial thromboplastin time, s	31.8 (30.6–34.8)	31.3 (29.7–33.5)	1.128	0.259
Thrombin time, s	16.1 (15.7–16.6)	16.6 (15.9–17.1)	–1.766	0.077
Fibrinogen, g/L	3.9 (3.6–4.6)	3.5 (3.1–4.2)	2.875	0.004

Data are the median (IQR) or n (%). P values comparing the changes in hemoglobin < -8g/L group and changes in hemoglobin ≥ -8g/L group are from the χ 2 test or nonparametric test.
*Fisher exact test. All laboratory findings were the values before treatment.
LMWH = low molecular weight heparin, NA = not applicable.

hemoglobin. We postulated that the decrease in hemoglobin at the beginning of the study might be related to confounding factors.

Numerous limitations remain in this investigation. First, due to the retrospective design, we could not control the time intervals between assessments of various indices in patients and the LMWH treatment schedule. Similarly, we could not predict and regulate the effective dose and time of LMWH. Second, some critical indicators were not identified and examined, including arterial gas analysis and T lymphocyte subset. Finally, the findings are constrained by the study small sample size and single-center methodology.

In conclusion, the preventive usage of LMWH did not lower hemoglobin in nonsevere COVID-19 patients with pneumonia. We consider using LMWH in COVID-19 patients safe and without significant adverse effects.

Table 4

Multivariate logistic regression analysis of correlative factors of hemoglobin change (Forward, LR, α = 0.05).

Item	β	SE	Wald	P	OR	95%CI
Fever	–1.500	0.447	11.241	0.001	0.223	0.093–0.536
Diabetes	–2.292	0.923	6.172	0.013	0.101	0.017–0.616
Pulse	0.007	0.013	0.270	0.604	1.007	0.981–1.033
Glucocorticoid	–1.163	1.246	0.871	0.351	0.313	0.027–3.594
LMWH	–0.172	0.394	0.192	0.661	0.842	0.389–1.820
CT imaging score	0.038	0.039	0.914	0.339	1.038	0.961–1.121
Fibrinogen	0.293	0.218	1.810	0.179	1.341	0.875–2.056

The dependent variable is whether the change of hemoglobin is less than –8g/L. LMWH used or not, and other significant factors in nonparametric tests were used as independent variables.
LMWH = low molecular weight heparin, OR = odds ratio, CI = confidence interval.

Author contributions

Conception and design: P-Y Hong and X-B Zhang. Collection and assembly of data: M-H Huang, A-K Hu and H-Q Zeng. Data analysis and interpretation: P-Y Hong, X-B Zhang and Y-T Lai. Manuscript writing: All authors. Final approval of manuscript: All authors.

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