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 −6.0 g/L (IQR −10.8 to 1.0) in the LMWH group and −2.0 g/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.<sup>[1]</sup> Inflammation and thrombosis are linked to COVID-19.<sup>[2–5]</sup> Postmortem examinations of patients with COVID-19 revealed thrombosis in minor pulmonary vessels and extrapulmonary organs with no evidence of coronavirus penetration.<sup>[6]</sup> Both thrombotic and hemorrhagic pathologies should be taken into account in COVID-19.<sup>[7]</sup> In patients with COVID-19, anticoagulation was suggested as a mitigating strategy.<sup>[8–10]</sup> Low molecular weight heparin (LMWH) produces a significant anticoagulant effect by activating antithrombin and may increase the risk of bleeding events.<sup>[11]</sup>

Using LMWH as an initial anticoagulant has been proven to lower mortality by preventing the formation of microthrombi and pulmonary coagulopathy.<sup>[12]</sup> In critically ill COVID-19 patients, anticoagulant medication with LMWH reduced the incidence of thrombotic complications.<sup>[13,14]</sup> 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.<sup>[11]</sup> Nonetheless, little research has examined LMWH adverse consequences, such as anemia.
A considerable hemoglobin loss without overt bleeding is possible during the early postanticoagulation phase, unlike serious bleeding complications. 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.

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. 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) 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) 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.

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) 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.](image-url)
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, snuffle, and myalgia), pulse, respiratory rate, systolic pressure, diastolic pressure, a saturation of pulse oxygen at rest, treatment (Chinese traditional medicine, prone position, and glucocorticoid), CT imaging score, and fibrinogen between the changes in hemoglobin and LMWH. The confounding factors were excluded by binominal 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.

3.2. 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 \(-6.0 \text{ (IQR } -10.8 \text{ to } 1.0\) in the LMWH group and \(-2.0 \text{ (IQR } -7.0 \text{ to } 4.0\) in the control group \( P < .001 \), between-group difference, \(-5.0 \text{ g/L}; 95\% \text{ confidence interval, } -7.0 \text{ to } -3.0\), 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 \(< 8\text{gL}\) group and the changes in hemoglobin \(\geq 8\text{gL}\) group \( P < .05 \).

As shown in Table 4, hemoglobin decline was defined as a change in hemoglobin of <25 percent of a total patient \(-8\text{gL}\). 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. E. 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. Anticoagulation was recommended as a mitigating option because of the increased risk of macrovascular and microvascular thrombosis in individuals with COVID-19.

Heparins, particularly LMWH, are preferred in hospitalized patients. LMWH is accessible and exposes healthcare personnel to COVID-19 patients less invasively. Numerous undesirable consequences of heparin treatment are associated with heparin broad biological activity, providing significant concerns. Bleeding is the primary safety risk associated with heparin usage. Mattioli, Benfarenos 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. Rentsch, Beckman 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. 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) | χ²/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/m²)     | 23.8 (21.6–26.5)    | 22.0 (19.7–24.4) | −3.237      | 0.001   |
| Comorbidty      |                     |                 |             |         |
| 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%)          | 40 (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%)      | 2.351       | 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 (96.0–99.0) | −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) | 29.0 (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, ×10⁹/L | 5.0 (4.3–6.7) | 5.3 (4.3–6.7) | −0.778      | 0.436   |
| *Neutrophil count, ×10⁹/L | 3.2 (2.3–4.9) | 3.3 (2.3–4.3) | 0.210       | 0.834   |
| *Lymphocyte count, ×10⁹/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, ×10⁹/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 (2.0–20.3) | 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) | χ²/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, μmoI/L | 69.0 (56.0–81.5) | 69.5 (59.3–82.5) | 1.726 | 0.084 |
| Lactic dehydrogenase, U/L | 160.0 (145.5–184.0) | 170.0 (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 (6.3–36.3) | 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 |
| Leukocyte count, ×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) | 2.0 (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 (28.0–33.0) | 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 | 182.0 (155.0–218.0) | 162.0 (141.5–179.5) | 3.561 | 0.000 |
| D-dimer, μg/mL | 10.8 (3.6–19.9) | 4.4 (1.1–10.7) | −3.784 | 0.000 |
| Creatine kinase, U/L | 58.0 (43.0–99.0) | 62.0 (50.0–81.8) | −0.665 | 0.508 |
| 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 | 36.0 (35.0–41.0) | 41.0 (39.0–43.0) | −5.603 | 0.000 |
| 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) | 4.395 | 0.000 |
| Creatinine, μmoI/L | 70.0 (55.0–84.0) | 70.0 (55.0–84.0) | 3.561 | 0.000 |
| Lactic dehydrogenase, U/L | 182.0 (155.0–218.0) | 162.0 (141.5–179.5) | 3.561 | 0.000 |
| C-reactive protein, mg/L | 10.8 (3.6–19.9) | 4.4 (1.1–10.7) | 3.784 | 0.000 |
| Creatine kinase, U/L | 419.3 (287.0–459.6) | 319.3 (87.3–437.2) | 3.569 | 0.000 |
| Creatine kinase MB, U/L | 1.5 (1.5–5.6) | 1.5 (1.5–5.6) | 2.541 | 0.011 |
| Total bilirubin, μmol/L | 36.0 (35.0–41.0) | 41.0 (39.0–43.0) | −5.603 | 0.000 |
| 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) | 4.395 | 0.000 |
| Creatinine, μmoI/L | 70.0 (55.0–84.0) | 70.0 (55.0–84.0) | 3.561 | 0.000 |
| Lactic dehydrogenase, U/L | 182.0 (155.0–218.0) | 162.0 (141.5–179.5) | 3.561 | 0.000 |
| C-reactive protein, mg/L | 10.8 (3.6–19.9) | 4.4 (1.1–10.7) | 3.784 | 0.000 |
| Creatine kinase, U/L | 419.3 (287.0–459.6) | 319.3 (87.3–437.2) | 3.569 | 0.000 |
| Creatine kinase MB, U/L | 1.5 (1.5–5.6) | 1.5 (1.5–5.6) | 2.541 | 0.011 |
| Total bilirubin, μmol/L | 36.0 (35.0–41.0) | 41.0 (39.0–43.0) | −5.603 | 0.000 |
| 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) | 4.395 | 0.000 |
| Creatinine, μmoI/L | 70.0 (55.0–84.0) | 70.0 (55.0–84.0) | 3.561 | 0.000 |
| Lactic dehydrogenase, U/L | 182.0 (155.0–218.0) | 162.0 (141.5–179.5) | 3.561 | 0.000 |

Data are the median (IQR) or n (%). P values comparing the LMWH group and control group are from the χ² 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.
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| 0.247   |
| Pharyngalgia                         | 0.088 | 0.902   |
| Pharyngovenositis                    | 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.
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 3
Potential factors associated with hemoglobin change.

| Characteristics                  | Changes in hemoglobin < −8g/L group (n = 43) | Changes in hemoglobin ≥ −8g/L group (n = 136) | χ²/Z value | P value |
|----------------------------------|-----------------------------------------------|-----------------------------------------------|------------|---------|
| Age, years, 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/m²)                      | 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                                             |            |         |
| Chronic obstructive pulmonary disease | 0                                      | 0                                             |            |         |
| 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   |
| Pharyngalia                      | 8 (18.6%)                                     | 32 (23.5%)                                    | 0.457      | 0.499   |
| Pharyngoxerosis                  | 14 (32.6%)                                    | 32 (23.5%)                                    | 1.398      | 0.238   |
| Sniffle                          | 2 (4.7%)                                      | 16 (11.6%)                                    | 1.126      | 0.289   |
| Myalgia                          | 5 (11.6%)                                     | 20 (14.7%)                                    | 0.298      | 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 (97.0–98.0)                              | 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%)                                   | NA         | NA      |
| 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, ×10³/μL                | 182.0 (146.0–216.0)                           | 203.0 (186.0–231.8)                           | −1.180     | 0.239   |
| 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 χ² test or nonparametric test.

*Fisher exact test. All laboratory findings were the values before treatment.

LMWH = low molecular weight heparin, NA = not applicable.

### 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 | 0.331 | 0.739 | 1.038 | 0.961–1.121   |
| Fibrinogen, g/L                   | 0.293 | 0.218 | 1.810 | 0.179 | 1.341 | 0.875–2.056   |

The dependent variable is whether the change of hemoglobin is < −8g/L and changes in hemoglobin ≥ −8g/L were from the χ² test or nonparametric test.

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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