Clinical observations of low molecular weight heparin in relieving inflammation in COVID-19 patients: A retrospective cohort study

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Abstract:

Background On March 11, 2020, the World Health Organization declared its assessment of COVID-19 as a global pandemic. Effective therapeutic drugs are urgently needed to improve the overall prognosis of patients, but currently no such drugs are available.

Methods Patients in the study were divided into a heparin and a control group based on whether low molecular weight heparin (LMWH) was used. D-dimer, C-reactive protein (CRP), peripheral blood lymphocyte percentage, interleukin-6, and other indices in 42 patients with novel coronavirus pneumonia were retrospectively analyzed to compare and evaluate the progress of patients before and after LMWH treatment.

Results Compared to the control group, D-dimer levels in the heparin group significantly increased before treatment, and there was no significant difference after treatment. There was no significant difference in the change of CRP levels between the two groups of patients before and after LMWH treatment, and levels for both groups were significantly lower after, compared to before, treatment. Compared to the control group, patients in the heparin group had a higher percentage of lymphocytes after treatment and lower levels of interleukin-6; these differences were statistically significant.

Conclusions Under conventional antiviral treatment regimens, LMWH can improve hypercoagulability, inhibit IL-6 release, and counteract IL-6 biological activity in patients. LMWH has potential antiviral effects and can help delay or block inflammatory cytokine storms. It can also increase the lymphocytes (LYM%)of patients and has the potential for treatment of COVID-19.

Introduction

Coronavirus is an enveloped, non-segmented, positive-sense, single-stranded RNA virus that causes common colds and severe respiratory diseases, [1]such as Middle East respiratory syndrome (MERS)[2] and severe acute respiratory syndrome (SARS)[2]. In December 2019, a series of unexplained pneumonia cases appeared in Wuhan, Hubei

Province, China, and their clinical manifestations suggested viral pneumonia.[4] Deep sequencing of lower respiratory tract samples identified a novel coronavirus named SARS-CoV-2 and the disease it caused was named COVID-19.[5] Its clinical manifestations include fever, cough, sputum, chest distress or asthma, fatigue, myalgia, diarrhea, nausea, and vomiting.[6,7,8] Severe cases may progress rapidly to acute respiratory distress syndrome, metabolic acidosis, septic shock, coagulopathy, and organ failure (e.g., liver, kidneys, and heart), which all pose a serious threat to human health.

On March 11, 2020, the World Health Organization (WHO) declared its assessment of COVID-19 as a global pandemic. SARS-CoV-2 is characterized by a long incubation period, high infectivity, and multiple routes of transmission.[9,10] According to real-time WHO statistics, the total number of confirmed cases of COVID-19 worldwide as of March 28, 2020 has exceeded 600,000, with more than 28,000 deaths. However, no effective medicines are currently available, and it can only be treated symptomatically. As the worldwide patient base continues to expand and the number of severely and critically ill patients increases rapidly, determining the mechanism through which patients progress from mild to severe and from severe to critical is the main avenue for discovering effective treatment strategies.

Lymphopenia and inflammatory cytokine storms are typical abnormalities observed in highly pathogenic coronavirus infections (such as SARS and MERS),[12] and are believed to be associated with disease severity.[12,13,14] Multiple studies have shown that cytokine storms are important mechanisms of disease exacerbation and death in patients with COVID-19.[12,13,14] IL-6 levels are significantly higher in severely ill patients with COVID-19 compared to those with mild cases.[15] A cytokine storm may occur when cytokines reach a certain threshold in the body.[16] Reducing the release or activity of IL-6 can prevent or even reverse the cytokine storm syndrome caused by the virus, thereby improving the condition of patients with COVID-19.

In recent years, a large number of studies have revealed that low molecular weight heparin (LMWH) has various non-anticoagulant properties that play an anti-inflammatory role by reducing the release and biological activity of IL-6.[17,18,19]

However, the anti-inflammatory effects of LMWH in COVID-19 are not currently known. To the best of our knowledge, this is the first retrospective cohort study, to analyze the relieving effect of LMWH in patients with COVID-19. This study aims to review and analyze the treatment course of patients with COVID-19 to investigate the anti-inflammatory effects of heparin and delay disease progression to provide guidance for subsequent clinical practice.

Methods

Research subjects

All cases in this study were located at Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, Hubei Province, China), a designated treatment hospital for patients with COVID-19. This study was approved by the institutional review board of the hospital. In total, 42 patients with COVID-19 treated at the hospital between February 1 and March 15, 2020 were selected for the study (Figure 1 shows the case inclusion flowchart), of which 21 underwent LMWH treatment (Heparin group, Table 1), and 21 did not (Control), during hospitalization.

Inclusion criteria: (1) met the diagnostic standards of novel coronavirus pneumonia (7th edition) formulated by the National Health Commission of China; (2) experienced any of the following: shortness of breath, respiration rate(RR) $\geq$ 30 breaths/minute; resting oxygen saturation $\leq$ 93%; $PaO_2/FiO_2 \leq 300$ mmHg; lung imaging showing significant lesion progression by > 50% within 24-48 h, and a severe clinical classification; (3) age $\geq$ 18 years; (4) no previous history of bronchiectasis, bronchial asthma, or other respiratory diseases; (5) no immunosuppressant or glucocorticoid use during treatment.

Exclusion criteria: (1) patients with severe systemic diseases and other acute or chronic infectious diseases; (2) patients with liver and kidney insufficiency or congenital heart disease; (3) patients who had been treated with LMWH in the previous three months; (4) patients with a previous history of mental illness; (5) pregnant or lactating women; (6) patients clinically classified as critically ill or housed in the intensive care unit (ICU); (7) patients allergic to LMWH or contraindicated for LMWH.

Data collection

Basic patient information collected in this study from electronic medical records included complete blood count, coagulation function, cytokines, serum biochemical tests (including liver function, kidney function, lactate dehydrogenase, C-reactive protein (CRP), and electrolytes), and disease progression. Two researchers also independently reviewed the data collected forms to double check the data collected.

Statistical analysis

Data analysis was performed using SPSS 22.0 statistical software. Data were expressed as mean ± standard deviation (SD). GraphPad 6.0 software was used for plotting. Differences between groups were evaluated using the T-test for measurement data, the chi-square test for count data, and the Kruskal-Wallis nonparametric test between groups (independent samples) and within groups (related samples). Differences of $p < 0.05$ were considered statistically significant.

Results

General characteristics of patients with COVID-19

As shown in Table 2, the heparin group consisted of 13 males and eight females aged between 42 and 91 years (median age was 69.0 years), and the control group consisted of 14 males and seven females aged between 40 and 84 years (median age was 69.0 years); there was no significant difference between the two groups. There were no significant differences in comorbidities, such as hypertension, diabetes, cardiovascular disease, and carcinomas, between the two groups. Similarly, there were no significant differences in novel coronavirus pneumonia onset symptoms, including fever (body temperature ≥ 37.3°C), cough, sputum, chest distress or asthma, myalgia, fatigue, anorexia, diarrhea, and nausea and vomiting. Similarly, there was no significant difference in antiviral treatment between the two groups. These results indicate that the general characteristics of the two groups of patients were consistent and comparable.

LMWH has no effect on the days to conversion to negative and the duration of hospitalization of patients with COVID-19

As shown in Table 2, the number of days to conversion to negative (time from

hospitalization to virus shedding) was 20.0 days (IQR 11.0-31.0) in the heparin group and 19.0 days (IQR 12.0-30.0) in the control group (p = 0.46); the difference between the two groups was not significant. Similarly, the length of hospital stay was 29.0 days (IQR 17.0-42.0) in the heparin group and 27.0 days (IQR 24.0-31.0) in the control group (p = 0.41); the difference between the two groups was not significant. Notably, all patients showed improvement after treatment.

Effect of LMWH on Blood routine in patients with COVID-19

As shown in Figure 2A-F, there was no significant difference in lymphocyte percentage between the heparin and control groups before and after LMWH treatment. However, patients in the heparin group had a significantly increased percentage of lymphocytes after LMWH treatment. In addition, the changes in lymphocyte percentages in patients in the heparin group before and after LMWH treatment were significantly different to those in the control group. The results suggest that LMWH increases lymphocyte percentage in patients with COVID-19, indicating that LMWH has some anti-inflammatory effects.

Compared with the control group, platelets were significantly increased after LMWH treatment. Similarly, the changes in platelet levels before and after LMWH treatment in the heparin group were significantly different from those in the control group. However, there was no significant difference in RBC, WBC, neutrophil% and monocyte% levels between the two groups.

Effect of LMWH on coagulation function in patients with COVID-19

As shown in Figure 2G-N, before patients were administered LMWH, the levels of D-dimer and fibrinogen degradation products (FDP) in patients in the heparin group were significantly higher compared to those in the control group, indicating that these patients may have been in a hypercoagulable state. After the administration of LMWH, D-dimer and FDP levels in the heparin group significantly decreased, and there was no significant difference with the control group. The D-dimer and FDP levels of patients in the heparin group before and after LMWH administration were significantly different. The results indicate that LMWH improves the hypercoagulable state in patients with COVID-19. However, there was no significant difference in TT,

APTT, PT, FIB, ATⅢ and INR levels between the two groups.

Effect of LMWH on CRP in patients with COVID-19

As shown in Figure 2O, there were no significant differences in CRP levels between the two groups of patients before and after LMWH treatment, and both were significantly lower compared to before treatment. Similarly, there were no significant differences in CRP levels between the two groups of patients.

Effect of LMWH on cytokines in patients with COVID-19

To further investigate the anti-inflammatory effects of LMWH, we performed statistical analyses on the levels of inflammatory cytokines in the two groups (Figure 3). There were no significant differences between the levels of IL-2, IL-4, IL-10, TNF-α, and IFN-γ in the heparin group and those of the control group before and after LMWH treatment. Similarly, the changes in IL-2, IL-4, IL-10, TNF-α, and IFN-γ levels were not significantly different between the two groups.

Notably, there was no significant difference in IL-6 levels between the heparin and control groups before LMWH treatment. After LMWH treatment, IL-6 levels in the heparin group were significantly reduced compared to the control group. Similarly, the changes in IL-6 levels in the heparin group before and after LMWH treatment were significantly different to those in the control group. The results suggest that the anti-inflammatory effects of LMWH may be associated with the reduction of IL-6 levels in patients with COVID-19.

Discussion

On March 11, 2020, the WHO declared its assessment of COVID-19 as a global pandemic. Although its case fatality rate is only 2.27%,[12] the number of severely and critically ill patients is increasing rapidly as the global patient base continues to expand. Studies have shown that cytokine storms are associated with deterioration in several infectious diseases, including SARS and avian influenza.[20] Cytokine storms are an important mechanism of exacerbation in patients.[21] In recent years, numerous studies have revealed that heparin has various non-anticoagulant properties. LMWH can exert anti-inflammatory effects by reducing the release and biological activity of IL-6. However, the anti-inflammatory effects of heparin in COVID-19 are not yet

known. The present study is, to the best of our knowledge, the first retrospective cohort study to analyze the relieving effect of LMWH in patients with COVID-19. This study aims to review and analyze the treatment course of the patients to investigate the anti-inflammatory effects of heparin and delay COVID-19 disease progression to provide guidance for subsequent clinical practice.

Von Willebrand Factor (VWF) can act as a bridge between vascular wall endothelial tissue and platelets, promoting platelet adhesion.Previous studies have shown that VWF level increased[22] and platelet level decreased[23] in SARS-CoV patients, suggesting that SARS-CoV-2 infection may promote the process of platelet thrombogenesis, thereby activating the subsequent coagulation cascade. At the same time, studies have shown that LMWH is not easily inactivated by Platelet Factor 4(PF4)[24,25], and has a strong affinity with VWF, which can prevent the interaction between VWF and platelet[26,27], significantly reduce the release of VWF[28] by platelet and endothelial cells, and reduce platelet aggregation and consumption. In the difference analysis of this study, the mean difference of platelet count in heparin group and control group was 5.57, -52.48($P < 0.05$), which was consistent with the results of the above study.

Clinical observations have shown that nearly 20% of patients with COVID-19 have coagulopathy, including nearly all severe and critically ill patients.[7,29] Studies have shown that IL-6 and IL-8 can cause hypercoagulation, leading to scattered fibrin clots, shortening the clot dissolution time and maximum dissolution rate,[30] which suggests that the hypercoagulation status of COVID-19 patients may be related to the body increased cytokine levels. In previous studies of patients with COVID-19, D-dimer levels were significantly elevated in patients admitted to the ICU with severe cases.[31] The research of Ning Tang et al. showed higher levels of d-dimer and FDP in fatal cases,[32] but Li *et al.* believe that while monitoring for venous thromboembolism, the correlation between D-dimer and COVID-19 severity must be considered.[33] However, there is currently no conclusive evidence supporting the use of D-dimer as an evaluation index.[34.35.36] A large sample analysis is required to determine whether D-dimer is associated with COVID-19 severity. Therefore, the present study does not

consider this parameter as an evaluation index for disease progression. The average values of d-dimer and FDP before treatment was greater in the heparin group than in the control group (3.75,1.23,$P < 0.01$;14.35,4.05,$P < 0.01$). This result is consistent with the goals of LMWH treatment in the heparin group. The analysis of differences showed that LMWH has a better effect on lowering D-dimer and FDP levels.

Several studies have recommended CRP and lymphocytes (LYM%)as indices for evaluating the effectiveness of clinical drugs or treatments.[37,38,39] In the analysis of differences in the present study, there was no statistically significant difference in CRP between the groups, indicating that LMWH treatment has no effect on this parameter. In the analysis of differences of LYM%, the mean value of the heparin group was higher than that of the control group (11.10% and 3.08%, respectively). LYM% was higher in the heparin group after treatment compared to the control group ($p < 0.001$), which is consistent with the results of Derhaschnig *et al.*[40] This suggests that LMWH can increase LYM% in patients with COVID-19 and improve their condition. There are two possible reasons for this; on one hand, LMWH is a glycosaminoglycan[41]that partially inhibits the SARS-related coronavirus strain HSR1.[42] Mycroft-West *et al.* also showed that LMWH can bind to the SARS-CoV-2 surface protein (Spike) S1 Receptor Binding Domain and block the replication of the virus, thus, showing potential antiviral effects.[43] Additionally, LMWH can reduce lymphocyte death caused by the direct viral infection of lymphocytes.[13] On the other hand, preliminary research has confirmed that proinflammatory cytokines, such as TNFα and IL-6, can induce lymphopenia.[14] Therefore, decreases in the number or activity of relevant inflammatory factors may have some significance for the increase in LYM%.

Studies have shown that cytokine storms are important mechanisms of exacerbation in patients.[21] IL-6 levels in severely ill patients with COVID-19 are significantly higher than in patients with mild cases,[15] and a cytokine storm may occur when cytokines reach a certain threshold in the body.[16] The transition from a mild to severe condition in patients with COVID-19 may be caused by cytokine storms. Reducing IL-6 release or activity can prevent or even reverse the cytokine storm syndrome caused by the

virus,[44] thereby improving the condition of patients with COVID-19. LMWH has a number of non-anticoagulant properties.[45] Multiple studies have shown that LMWH may reduce the release of IL-6 in the body by regulating plasma AT[46] or APC[47] levels and inhibiting the expression of nuclear factor κB (NF-κB).[17,18,19] In the present study, we performed statistical analysis of the levels of inflammatory cytokines in two groups of patients, and the results showed that IL-6 significantly decreased in the heparin group compared to the control group, whereas the changes in other inflammatory factors were not statistically significant; these results are consistent with the conclusions above. In addition, a study by Mummery *et al.* found that LMWH can bind to IL-6, competitively reduce the binding of IL-6 to SIL-6R and sgp130,[48] and block signal transduction, thereby inhibiting the biological activity of IL-6. This indicates that LMWH reduces the release of IL-6 while also reducing its biological activity, which also explains the increase of LYM% in the heparin group.

The present study found that under conventional antiviral treatment regimens, LMWH could improve hypercoagulability, inhibit IL-6 release, and inhibit IL-6 biological activity in patients. LMWH has potential antiviral effects, helps delay or block inflammatory cytokine storms, increases LYM%, and may be suitable for COVID-19 treatment. In addition, to further confirm the conclusions of this study, we conducted a prospective clinical study to evaluate the efficacy and safety of enoxaparin sodium in the treatment of hospitalized adult patients with COVID-19（Chinese Clinical Trial Registry， number:chiCTR2000030700）, with the expectation of providing a more powerful reference for treatment.

Limitations:

This study has some limitations. First, due to the retrospective design, we were unable to control the time intervals between examinations of various indices in patients and the LMWH dosing schedule, and we could not estimate the effective dose and timing of LMWH. Second, there were no critical cases in the two groups of patients in the trial; the treatment outcome of all cases was improvement and discharge and there were no deaths. Therefore, the reference value for the treatment outcomes of critically ill patients was limited. Finally, the sample size and single-center design may have

limited our findings.

Contributors

CS, JP and YZ conceptualized and designed the study, and CS and YZ had full access to all data, and took responsibility for data integrity and accuracy of the analysis. CS, CW and HX wrote the manuscript. CY, FC and FZ reviewed the manuscript. FC, YH, TT and BD performed the statistical analysis. All authors contributed to data acquisition, analysis and interpretation, and approved the final version for submission.

Declaration of interests

All authors declare no competing interests.

Data Availability Statement

The data used to support the findings of this study are included within the article.

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Patient consent for publication Not required

Ethics approval The human study was approved the Research Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

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Figure captions

Figure 1. Flowchart of inclusion and exclusion criteria for patients with COVID-19

Based on strict inclusion and exclusion criteria, 42 patients with COVID-19 treated at the hospital between February 1 and March 15, 2020 were selected for the study, of which 21 underwent LMWH treatment (Heparin group) and 21 did not (Control) during hospitalization.

Table 1. LMWH use in the 21 patients with COVID-19

Details of the dose, frequency, route of administration, and days of use of LMWH in the heparin group.

Table 2. General characteristics of all the patients with COVID-19

There were no significant differences in age, sex, comorbidities, onset symptoms, time from hospitalization to virus shedding, length of hospital stay, antiviral treatment and disease progression between the two groups. Data are median (IQR) or n(%). p values are comparing heparin group and control. NA=not applicable.

Figure 2. Effect of LMWH on Blood routine, coagulation function and CRP in patients with COVID-19.

(A-O) Red blood cells (A), platelets (B), white blood cells (C), neutrophils% (D) ,lymphocytes% (E), monocytes% (F), TT (G), APTT (H), PT (I), D-dimer (J), FIB (K), FDP (L), AT III (M), INR (N), and CRP (O) levels in patients with COVID-19. Data are expressed as mean ± standard deviation (SD) (n = 21). C1 vs. H1 or C2 vs. H2, ^{a} $p < 0.05$, ^{aa} $p < 0.01$, ^{aaa} $p < 0.001$; C1 vs. C2 or H1 vs. H2, ^{b} $p < 0.05$, ^{bb} $p < 0.01$, ^{bbb} $p < 0.001$; C3 vs. H3, ^{c} $p < 0.05$, ^{cc} $p < 0.01$, ^{ccc} $p < 0.001$. (C1: control group, indices at admission; C2: control group, indices at discharge; C3: control group, changes in indices during hospitalization; H1: heparin group, indices before LMWH treatment; H2: heparin group, indices after LMWH treatment; H3: heparin group, changes in indices before and after LMWH treatment.)

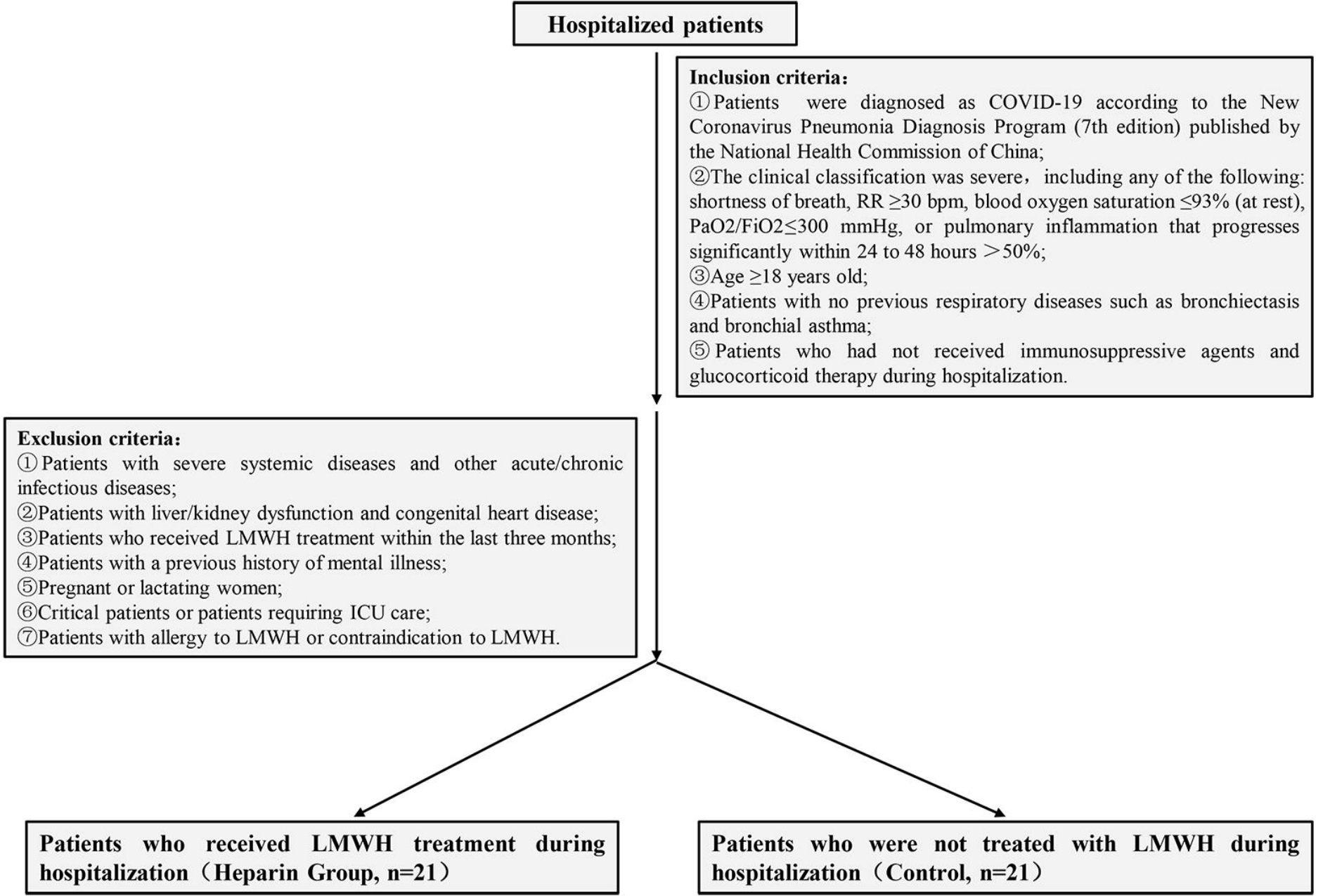
Figure 3. Effect of LMWH on inflammatory cytokines in patients with COVID-19

(A-F) IL-2 (A), IL-6 (B), TNF-α (C), IL-4 (D), IL-10 (E), and IFN-γ (F) levels in the

two groups of patients with COVID-19. Data are expressed as mean ± standard deviation (SD) (n = 21). ^{a} $p < 0.05$, ^{aa} $p < 0.01$, ^{aaa} $p < 0.001$; C1 vs. C2 or H1 vs. H2, ^{b} $p < 0.05$, ^{bb} $p < 0.01$, ^{bbb} $p < 0.001$; C3 vs. H3, ^{c} $p < 0.05$, ^{cc} $p < 0.01$, ^{ccc} $p < 0.001$. (C1: control group, indices at admission; C2: control group, indices at discharge; C3: control group, changes in indices during hospitalization; H1: heparin group, indices before LMWH treatment; H2: heparin group, indices after LMWH treatment; H3: heparin group, changes in indices before and after LMWH treatment.)

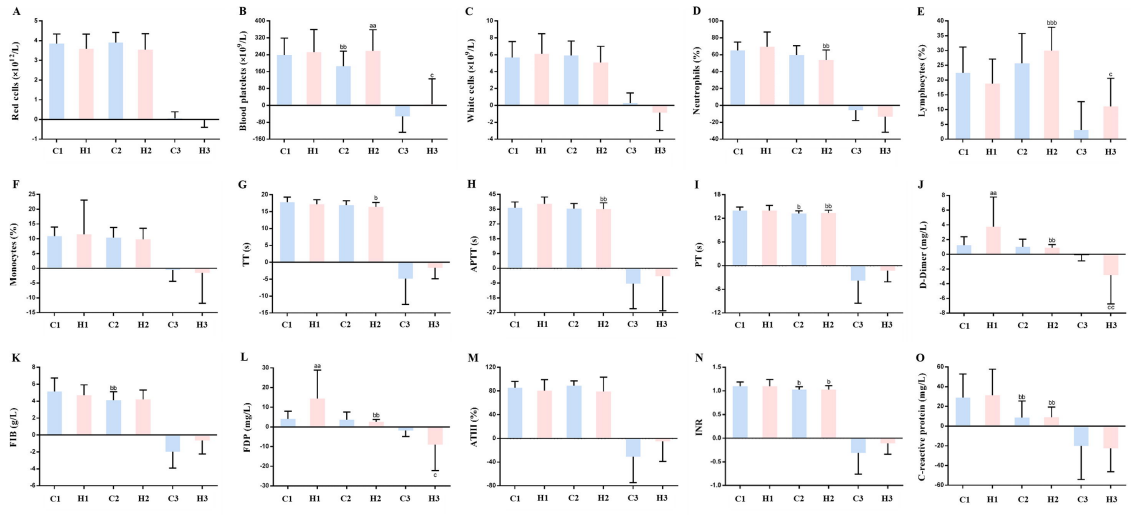
Figure 4. Possible mechanism of anti-inflammatory effects of LMWH in patients with COVID-19

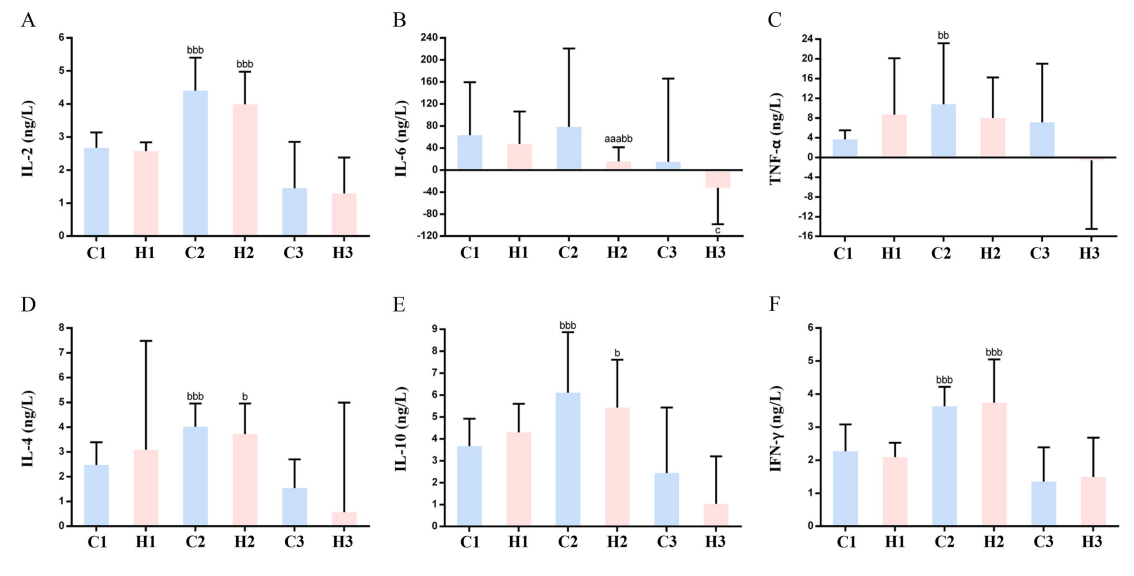
Under conventional antiviral treatment regimens, LMWH improves hypercoagulability, inhibits IL-6 release, and counteracts IL-6 biological activity in patients. It has potential antiviral effects and helps delay or block inflammatory cytokine storms. LMWH can increase the LYM% of patients and may be suitable as treatment for COVID-19.

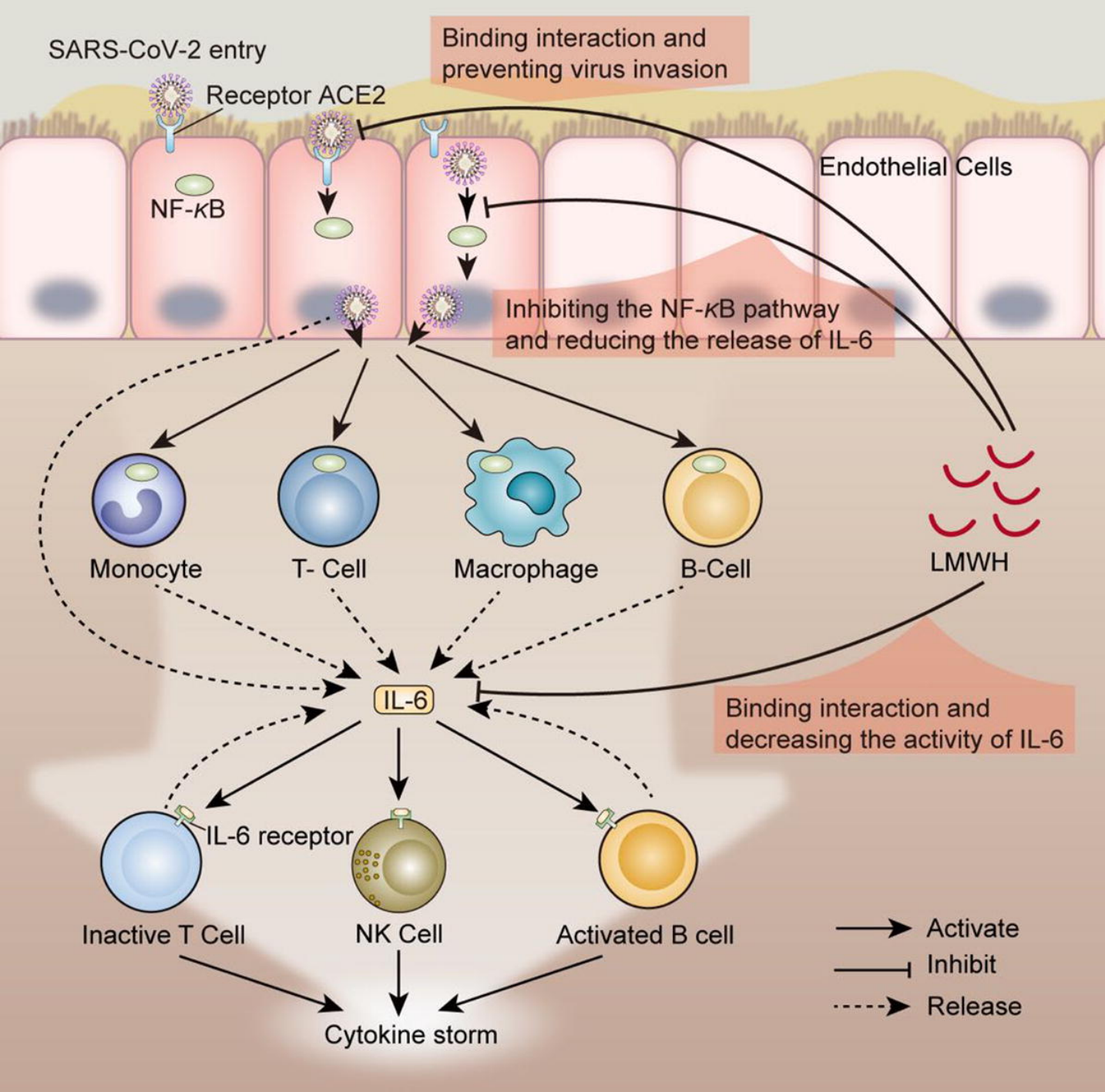

Hospitalized patients
Inclusion criteria:
① Patients were diagnosed as COVID-19 according to the New Coronavirus Pneumonia Diagnosis Program (7th edition) published by the National Health Commission of China;
②The clinical classification was severe, including any of the following: shortness of breath, RR ≥30 bpm, blood oxygen saturation ≤93% (at rest), PaO2/FiO2≤300 mmHg, or pulmonary inflammation that progresses significantly within 24 to 48 hours ＞50%;
③Age ≥18 years old;
④Patients with no previous respiratory diseases such as bronchiectasis and bronchial asthma;
⑤ Patients who had not received immunosuppressive agents and glucocorticoid therapy during hospitalization.
Exclusion criteria:
① Patients with severe systemic diseases and other acute/chronic infectious diseases;
②Patients with liver/kidney dysfunction and congenital heart disease;
③Patients who received LMWH treatment within the last three months;
④Patients with a previous history of mental illness;
⑤Pregnant or lactating women;
⑥Critical patients or patients requiring ICU care;
⑦Patients with allergy to LMWH or contraindication to LMWH.
Patients who received LMWH treatment during hospitalization（Heparin Group, n=21）
Patients who were not treated with LMWH during hospitalization（Control, n=21）

Heparin Group (n=21)	Treatment with LMWH	Days of treatment
H1	Enoxaparin sodium injection 4000AxaIU qd i.h.	10
H2	Enoxaparin sodium injection 4000AxaIU qd i.h.	10
H3	Enoxaparin sodium injection 4000AxaIU qd i.h.	14
H4	Enoxaparin sodium injection 4000AxaIU qd i.h.	13
H5	Enoxaparin sodium injection 4000AxaIU qd i.h.	17
H6	Nadroparin calcium injection 4100AxaIU qd i.h.	9
H7	Enoxaparin sodium injection 4000AxaIU qd i.h.	2
H8	LMWH sodium injection 5000IU once i.h.	1
H9	Enoxaparin sodium injection 4000AxaIU qd i.h.	16
H10	Enoxaparin sodium injection 4000AxaIU qd i.h.	19
H11	Enoxaparin sodium injection 4000AxaIU qd i.h.	14
H12	Enoxaparin sodium injection 2000AxaIU qd i.h.	19
H13	Enoxaparin sodium injection 2000AxaIU qd i.h.	22
H14	Nadroparin calcium injection 4100AxaIU qd i.h.	11
H15	Nadroparin calcium injection 4100AxaIU qd i.h.	13
H16	Enoxaparin sodium injection 4000AxaIU qd i.h.	8
H17	Nadroparin calcium injection 4100AxaIU qd i.h.	19
H18	LMWH sodium injection 5000IU qd i.h.	8
H19	Enoxaparin sodium injection 4000AxaIU qd i.h.	8
H20	Enoxaparin sodium injection 4000AxaIU qd i.h.	7
H21	Enoxaparin sodium injection 4000AxaIU qd i.h.	10

	Heparin Group (n=21)	Control (n=21)	p value
Characteristics			
Age, years	69.0(42.0-91.0)	69.0(40.0-84.0)	0.54
Sex	-	-	0.75
Female	8(38%)	7(33%)	-
Male	13(62%)	14(67%)	-
Comorbidity	13(62%)	8(38%)	0.12
Hypertension	8(38%)	5(24%)	0.32
Diabetes	6(29%)	2(10%)	0.12
Cardiovascular disease	5(24%)	2(10%)	0.21
Chronic obstructive lung disease	0	0	NA
Carcinoma	0	1(5%)	0.31
Chronic kidney disease	0	0	NA
Other	4(19%)	1(5%)	0.15
Signs and symptoms			
Fever (temperature ⩾37.3℃)	15(71%)	13(62%)	0.51
Cough	9(43%)	7(33%)	0.53
Sputum	6(29%)	4(19%)	0.47
Chest distress or asthma	11(52%)	8(38%)	0.35
Myalgia	2(10%)	3(14%)	0.63
Fatigue	8(38%)	5(24%)	0.32
Anorexia	6(29%)	5(24%)	0.73
Diarrhoea	2(10%)	1(5%)	0.55
Nausea or vomiting	2(10%)	1(5%)	0.55
Respiratory rate ⩾30 breaths per min	0	0	NA
Pulse ⩾125 beats per min	0	0	NA
Systolic blood pressure ＜90 mmHg	0	0	NA
Antiviral therapy			
Arbidol	18(86%)	20(95%)	0.29
Recombinant Human Interferon α2B (aerosol inhalation)	6(29%)	6(29%)	1.00
Ribavirin	2(10%)	0	0.15
Lopinavir/Ritonavir	2(10%)	0	0.15
Traditional Chinese medicine decoction	11(52%)	9(43%)	0.54
Disease progression			
Improved	21(100%)	21(100%)	NA
Invariable	0	0	NA
Deteriorative	0	0	NA
Time from hospitalization to virus shedding after the onset of the COVID-19, days	20.0(11.0-31.0)	19.0(12.0-30.0)	0.46
Hospital length of stay, days	29.0(17.0-42.0)	27.0(24.0-31.0)	0.41


A
Red cells (×10^12/L)
B
Blood platelets (×10^9/L)
C
White cells (×10^9/L)
D
Neutrophils (%)
E
Lymphocytes (%)
F
Monocytes (%)
G
TT (s)
H
APTT (s)
I
PT (s)
J
D-Dimer (mg/L)
K
FIB (g/L)
L
FDP (mg/L)
M
ATIII (%)
N
INR
O
C-reactive protein (mg/L)
C1
H1
C2
H2
C3
H3


A
IL-2 (ng/L)
bbb
bbb
C1
H1
C2
H2
C3
H3
B
IL-6 (ng/L)
aaabb
c
C
TNF-α (ng/L)
bb
D
IL-4 (ng/L)
bbb
b
E
IL-10 (ng/L)
bbb
b
F
IFN-γ (ng/L)
bbb
bbb


SARS-CoV-2 entry
Receptor ACE2
Binding interaction and preventing virus invasion
Endothelial Cells
NF-κB
Inhibiting the NF-κB pathway and reducing the release of IL-6
Monocyte
T- Cell
Macrophage
B-Cell
LMWH
IL-6
Binding interaction and decreasing the activity of IL-6
IL-6 receptor
Inactive T Cell
NK Cell
Activated B cell
Cytokine storm
Activate
Inhibit
Release