# Incidence and Risk Factors of Deep Vein Thrombosis in Hospitalized COVID-19 Patients

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## Abstract

Deep vein thrombosis (DVT) is prevalent in patients with coronavirus disease 2019 (COVID-19). However, the risk factors and incidence rate of DVT remains elusive. Here, we aimed to assess the incidence rate and risk factors of DVT. All patients diagnosed with COVID-19 and performed venous ultrasound by ultrasound deparament between December 2019 and April 2020 in Wuhan Jin Yin-tan hospital were enrolled. Demographic information and clinical features were retrospectively collected. Notably, a comparison between the DVT and the non-DVT groups was explored. The incidence rate of venous thrombosis was 35.2% (50 patients out of 142). Moreover, the location of thrombus at the proximal extremity veins was 5.6% (n = 8), while at distal extremity veins was 35.2% (n = 50) of the patients. We also noted that patients with DVT exhibited a high level of D-dimer (OR 10.9 (95% CI, 3.3-36.0), $P$ < 0.001), were admitted to the intensive care unit (OR 6.5 (95% CI, 2.1-20.3), $P$ = 0.001), a lower usage of the anticoagulant drugs (OR 3.0 (95% CI, 1.1-7.8), $P$ < 0.001). Finally, this study revealed that a high number of patients with COVID-19 developed DVT. This was observed particularly in critically ill patients with high D-dimer levels who required no anticoagulant medication.

## Introduction

Coronavirus disease 2019 (COVID-19) is a highly infectious disease that currently has been labeled as a global pandemic. The number of confirmed cases is rapidly increasing. For instance, as of July 30, 2020, more than 16.8 million cases had been reported worldwide with 662,095 deaths.[1] Notably, patients diagnosed with COVID-19 mainly showed respiratory symptoms,[2] while some developed coagulopathy which might be associated with poor outcomes.[3] Furthermore, the association between COVID-19 and venous thrombosis has not been explored. However, a distinctive feature of the 1918 influenza virus was widespread pulmonary thrombosis.[4] In particular, the thrombus formation was found to be the major cause in fatal cases.[5] Similar pathological changes have also been observed in other less-lethal pandemic studies or deaths associated with seasonal influenza outbreaks.[6] Besides, significant venous thrombosis conditions were observed in patients with H1N1.[7] Recently, a similar situation has been noted in patients with COVID-19. Particularly, coagulopathy is prevalent in COVID-19 patients, whereas the fibrinogen and D-dimers levels were higher than normal.[8] A previous study showed that 40% of patients were at high risk of developing venous thrombosis.[9] On the other hand, several risk factors for venous thrombosis such as immobilization, mechanical ventilation, and infection could be observed in patients with COVID-19.[2,10] Therefore, the diagnosis of DVT is imperative for optimal clinical

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management. However, during the pandemic outbreak, limited healthcare resources resulted in a lack of examination of DVT. Thus, it is important to investigate the incident and risk factors of DVT particularly in patients with COVID-19. Herein, we aimed to assess the incident and risk factors of venous thrombosis in COVID-19 patients by comparing the clinical features of DVT patients with non-DVT patients.

## Methods

### Study Design

This study was single centered, and retrospective, it was conducted at the pandemic epicenter in Jin Yin-tan hospital, Wuhan, China between December 2019 and April 2020. The patients were diagnosed for COVID-19 based on Diagnosis and Treatment Protocols for Patients with Novel Coronavirus Pneumonia provided by the National Health Commission of China. All the patients who underwent lower extremity venous ultrasound examinations by the ultrasound department were enrolled. However, whether the examinations were performed or not was decided by patients' physicians in charge. Overall, 157 patients with COVID-19 undertook venous ultrasound examinations during the study period. Nevertheless, 3 of the patients were excluded as they were diagnosed with venous thrombosis before infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Also, 12 patients were excluded due to incomplete ultrasound examinations or clinical data. Therefore, 142 patients were enrolled in this study. All identifiable information related to patients were de-identified before storage and analyses.

The lower extremity venous ultrasound examinations were conducted by specialized sonographers. All the patients were examined laying in a supine position with the legs extended. Then, the sonographer observed the common femoral vein plus the entire vein of the lower extremity directly using the compression method. Notably, if there were partial or complete incompressibility of a venous segment, we defined it as venous thrombosis. On the other hand, if there were positive signs in the extremity such as edema or swelling, the sonographer examined the veins more intensively. This study was approved by the Ethics Committee of Jin Yin-tan hospital (KY-2020-36.01) and written informed consent was waived.

### Data Collection and Definitions

Three physicians with at least five-year working experience, and had worked on the COVID-19 issues joined the study team at Jin Yin-tan hospital. Their responsibility was to collect data from the study patients including (1) demographic information such as gender, age, weight, height, date of onset of symptoms, and date of admission; (2) comorbidities; (3) vital signs and results of laboratory test on the ultrasound examined day. For the patient who undertook multiple ultrasound examinations at different time points, if there was a positive finding, the dates

on that point were recorded. Conversely, if there was no positive finding, the dates on the last negative day were noted; (4) the prophylaxis of venous thrombosis; and (5) outcomes. Finally, if there were questions or uncertainties during the data collection, the patients' physicians were involved to reach a consensus.

### Statistical Analysis

Data that followed the normal distribution were expressed as mean $\pm$ standard deviation. The comparison between the DVT and non-DVT groups was done using an independent sample T-test. On the other hand, data that did not follow the normal distribution were represented as median [interquartile range], while the comparison between the DVT and non-DVT groups was executed using the rank-sum test. Additionally, the categorical variables were expressed as count (%), whereas the differences between the DVT and non-DVT groups were explored using a chi-squared test. All statistical tests were 2-tailed with a significance level set at $P < 0.05$. To explore the risk factors associated with DVT, logistic regression models were used. Due to the limited number of cases and to avoid overfitting, only 3 variables were included in the model. These variables included the level of D-dimer, the admission of ICU, and the use of the anticoagulant drug. All data analyses were implemented using the SPSS software version 24.0 (IBM Corporation, USA).

## Results

### The Incidents and Location of DVT

Notably, 50 patients (35.2%) were diagnosed with DVT and, all had a thrombosis in the distal lower extremity veins, 8 of them showed a similar condition in the proximal lower extremity veins. Moreover, the location of thrombus in the left proximal lower extremity veins was 3.5% (n = 5), whereas in the left distal lower extremity veins was 26.8% (n = 38). On the other hand, in the right proximal lower extremity veins, the location was 2.1% (n = 3), while in the right distal lower extremity veins it was 27.5% (n = 39).

### Demographic Data and Comorbidities

The demographic data and clinical coexisting characteristics are presented in Table 1. Here, the mean age was 61.86 $\pm$ 12.43 years, and 81 (57.2%) patients were male. Out of the total, 83 (58.4%) patients were admitted to ICU. Moreover, 88 (62.0%) patients showed 1 or more coexisting conditions. The 3 most prevalent coexisting conditions were hypertension in 61 (43.0%), diabetes in 19 (13.4%), and coronary heart disease in 16 (11.3%) patients. Lastly, there were significantly more ICU patients in the DVT group than the non-DVT (90% vs 41.3%, $P < 0.001$). There was no coexisting disease was the risk factor of the DVT.

**Table 1.** Demographic Date and Preexisting Comorbidities in 142 Patients With COVID-19.

| Characteristics | Total (n = 142) | DVT group (n = 50) | Non-DVT group (n = 92) | P-value |
|---|---|---|---|---|
| Age, mean ± SD, years | 61.9 ± 12.4 | 64.0 ± 12.0 | 60.7 ± 12.6 | 0.138 |
| Age ≥70 | 30(21.1%) | 14(28%) | 16(17.4%) | 0.139 |
| Male | 81(57.2%) | 32(64%) | 49(53.2%) | 0.688 |
| ICU patients | 83(58.4%) | 45(90.0%) | 38(41.3%) | <0.000 |
| BMI index, mean ± SD | 23.5 ± 2.6 | 23.8 ± 2.4 | 23.8 ± 2.7 | 0.230 |
| Cannot walk before infection | 14(9.9%) | 7(14.0%) | 7(7.6%) | 0.222 |
| Hypertension | 61(43.0%) | 24(48.0%) | 37(40.2%) | 0.371 |
| Diabetes | 19(13.4%) | 7(14.0%) | 12(13.0%) | 0.873 |
| Hyperlipidemia | 4(2.8%) | 3(6.0%) | 1(1.1%) | 0.246 |
| Smoking | 9(6.3%) | 3(6.0%) | 6(6.5%) | >0.999 |
| Coronary heart disease | 16(11.3%) | 6(12.0%) | 10(10.9%) | 0.839 |
| Chronic nephrosis | 3(2.1%) | 1(2.0%) | 2(2.2%) | >0.999 |
| Malignancy tumor | 6(4.2%) | 2(4.0%) | 4(4.3%) | >0.999 |
| psychological disease | 4(2.8%) | 2(4.0%) | 2(2.2%) | 0.923 |
| Leukemia or lymphoma | 1(0.7%) | 1(2.0%) | 0 | 0.352 |
| Organ transplantation | 1(0.7%) | 0 | 1(1.1%) | >0.999 |
| Chronic obstructive pulmonary disease | 3(2.1%) | 1(2.0%) | 2(2.2%) | >0.999 |
| Asthma | 1(0.7%) | 0 | 1(1.1%) | >0.999 |
| Cerebrovascular disease | 6(4.2%) | 2(4.0%) | 4(4.3%) | >0.999 |
| Human immunodeficiency virus | 8(5.6%) | 0 | 8(8.7%) | 0.050 |
| Connective tissue disease | 1(0.7%) | 1(2.0%) | 0 | 0.352 |
| long-term corticoid or immunosuppressive therapy | 2(1.4%) | 1(2.0%) | 1(1.1%) | >0.999 |
| Chronic hepatopathy | 6(4.2%) | 3(6.0%) | 3(3.3%) | 0.735 |
| Alzheimer's disease | 1(0.7%) | 0 | 1(1.1%) | >0.999 |
| Atrial fibrillation | 2(1.4%) | 0 | 2(2.2%) | 0.541 |
| Varicosity | 3(2.1%) | 1(2.0%) | 2(2.2%) | >0.999 |
| Duration from onset of symptom to the current study, median [IQR], days | 40.0 [25.8-50] | 45.0 [34.3-53.0] | 28.5 [19.8-38.5] | <0.000 |
| Duration from hospital admission to the current study, median [IQR], days | 31.0 [17.8-39.3] | 33.0 [22.0-41.0] | 22.0 [14.0-32.0] | 0.001 |

Abbreviations: COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; SD, stand deviation; ICU, intensive care unit; IQR, interquartile range. Data are expressed as mean ± SD, median [interquartile range] or count (%).

## Vital Sign and Laboratory Tests on Ultrasound Examination Day

The vital sign and laboratory findings are shown in Table 2. The univariate analysis for comparison between the DVT and non-DVT groups, revealed significant differences in heart rate, systolic and diastolic blood pressure, respiratory rate, a saturation of pulse oxygen, counts of white blood cell, neutrophils and lymphocytes, the concentration of glutamic pyruvic transaminase and oxalacetic transaminase. Also in total bilirubin, albumin, blood urea nitrogen, creatine kinase MB (CK-MB) and hypersensitive troponin concentrations, prothrombin and activated partial thromboplastin times, fibrinogen, D-dimer, and myoglobin plasma concentration. Finally, in C-reactive protein, ferritin concentration, days of mechanical ventilation, rate of anticoagulant after ultrasound examinations, days of positive SARS-CoV-2 nucleic acid, and the number of deaths.

However, there were no significant statistical differences in hemoglobin concentration, hematocrit, serum creatinine concentration, activated pretrial thromboplastin time, procalcitonin, rate of anticoagulant before ultrasound examination, the days of positive SARA-CoV-2 nucleic acid, and rate of antiplatelet.

## The Logistic Regression Analysis and Risk Factors of DVT

The logistic regression analysis revealed that patients with DVT exhibited a high level of D-dimer (OR 10.9 (95% CI, 3.3-36.0), $P < 0.001$), and were admitted to the intensive care unit (OR 6.5 (95% CI, 2.1-20.3), $P = 0.001$). Thereby, resulting in lower usage of the anticoagulant drugs (OR 3.0 (95% CI, 1.1-7.8), $P < 0.001$) (Table 3).

Moreover, receiver operating characteristic (ROC) analysis showed that the use of the anticoagulant drug ($P = 0.571$, the area under curve = 0.471, 95% CI, 0.372–0.570) could not predict the occurrence of DVT. Conversely, we noted that the level of D-dimer ($P < 0.001$, the area under curve = 0.769, 95% CI, 0.690–0.848), admission to ICU ($P < 0.001$, the area under curve = 0.742, 95% CI, 0.660–0.825) and the logistic regression model ($P < 0.001$, the area under curve = 0.863, 95% CI, 0.801–0.925) may help to predict the presence of DVT (Figure 1).

## Discussion

In this retrospective study, we report the incidence and risk factors of venous thrombosis in COVID-19 patients. We found

**Table 2.** Vital Sings and Laboratory Test at the Ultrasound Examination Day, the Therapy and Outcome of the 142 COVID-19 Patients.

| Characteristics | Total (n=142) | DVT group (n=50) | Non-DVT group (n=92) | P-value |
|---|---|---|---|---|
| Heart rate (beat pre minute) | 85(80-101) | 89.5(84-102) | 84(78-100) | 0.031 |
| Systolic blood pressure (mmHg) | 124.5(113-136.3) | 121.5(111-130) | 127(116.5-138) | 0.039 |
| Diastolic blood pressure (mmHg) | 74(67-83) | 69.5(65-78) | 77.5(69-85) | 0.002 |
| Respiratory rate (breaths per minute) | 20(20-24) | 23(20-25) | 20(19-22) | <0.000 |
| Saturation of pulse oxygen (%) | 97(96-98) | 96(94-98) | 97(96-98) | 0.001 |
| White blood cell count (×10$^9$/L) | 7.5(5.5-12.7) | 11.8(7.0-18.9) | 6.8(5.2-8.6) | <0.000 |
| Neutrophils (×10$^9$/L) | 5.0(3.5-10.6) | 10.1(5.2-16.8) | 4.2(3.3-6.5) | <0.000 |
| Lymphocytes (×10$^9$/L) | 1.1(0.6 -1.6) | 0.6(0.4 -1.0) | 1.4(0.9-2.0) | <0.000 |
| Hemoglobin (g/L) | 112.0(93.5-122.3) | 108.0(89.0-118.0) | 114.0(96.0-125.5) | 0.092 |
| Hematocrit (%) | 34.0(29.6-36.8) | 33.8(29.0-35.5) | 34.2(30.3-37.8) | 0.190 |
| Platelets (×10$^9$/L) | 183.5(133-250) | 150(95-204) | 198.5(157-255) | <0.000 |
| Glutamic pyruvic transaminase (U/L) | 27(14.8-55.8) | 36(23-36) | 20.5(14-41.5) | 0.002 |
| Glutamic oxalacetic transaminase (U/L) | 29(22-44) | 35(27-58) | 26(21-34.5) | <0.000 |
| Total bilirubin concentration (μmol/L) | 11.4(9.3-16.5) | 15.6(10.5-23.2) | 10.7(8.7-13.7) | <0.000 |
| Albumin concentration (g/L) | 34.9(30.0-38.9) | 30.8(27.7-34.8) | 36.8(33.2-39.5) | <0.000 |
| Serum creatinine concentration (μmol /L) | 65.7(54.8-90.7) | 73.0(55.0-142.5) | 64.5(54.4-76.5) | 0.062 |
| Blood urea nitrogen (mmol /L) | 6.3(4.3-9.7) | 9.0(5.4-13.4) | 5.3(4.1-7.4) | <0.000 |
| CK-MB (U/L) | 11.0(8.0-16.8) | 12.0(8.0-23.3) | 10.0(8.0-13.0) | 0.034 |
| Hypersensitive troponin (pg/ml) | 10.3(2.7-33.1) | 31.9(9.1-73.2) | 4.4(1.7-17.9) | <0.000 |
| Prothrombin time (s) | 11.5(10.8-12.9) | 12.4(11.6-14.0) | 11.2(10.7-12.0) | <0.000 |
| Activated partial thromboplastin time (s) | 27.9(24.3-32.8) | 30.3(25.6-37.0) | 26.5(23.8-32.0) | 0.005 |
| Fibrinogen (g/L) | 2.9(2.2-4.3) | 3.8(2.8-5.9) | 2.7(2.1-3.5) | <0.000 |
| D-dimer (mg/L) | 2.6(0.7-9.3) | 9.0(4.6-22.9) | 1.1(0.4-3.7) | <0.000 |
| Myoglobin plasma concentration (ng/ml) | 46.9(28.4-127.8) | 109.7(34.5-211.3) | 35.5(23.6-60.9) | <0.000 |
| Procalcitonin (ng/ml) | 0.3(0.2 -1.8) | 0.3(0.1 -1.6) | 0.2(0.1-0.6) | 0.068 |
| C-reactive protein (mg/dL) | 12.0(1.6-42.9) | 27.8(3.1-79.2) | 2.3(0.8-21.7) | <0.000 |
| Ferritin concentration (μg/L) | 473.4(206.4-1437.9) | 1390.4(473.4-2000.0) | 274.2(156.2-603.9) | <0.000 |
| Mechanical ventilation | 64(45.1%) | 35(70.0%) | 29(31.5%) | <0.000 |
| Days of positive SARS-CoV-2 nucleic acid | 33(21-44) | 28.5(17.25-43.25) | 35(22-44) | 0.453 |
| Anticoagulant (before ultrasound examination) | 37(26.1%) | 11(22.0%) | 26(28.3%) | 0.417 |
| Anticoagulant (after ultrasound examination) | 71(50.0%) | 43(86.0%) | 28(30.4%) | <0.000 |
| Antiplatelet | 10(7.0%) | 6(12.0%) | 4(4.3%) | 0.174 |
| Number of deaths | 33(23.2%) | 27(54.0%) | 6(6.5%) | <0.000 |

Abbreviations: COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; CK-MB, creatine kinase-MB; SARS-CoV-2, severe acute respiratory coronavirus 2. Data are expressed as median (interquartile range) or count (%).

**Table 3.** Risk Factors of DVT in Patients With COVID-19 Using Logistic Regression Model.

| | OR (95% CI) | P |
|---|---|---|
| D-dimer (mg/L) | | |
| <2 | 1.00 | |
| ≥2 | 10.9(3.3-36.0) | 0.000 |
| Clinical type | | |
| ICU patients | 1 | |
| Non-ICU patients | 6.5(2.1-20.3) | 0.001 |
| Anticoagulation | | |
| Yes | 1 | |
| No | 3.0(1.1-7.8) | 0.025 |

Abbreviations: DVT, deep vein thrombosis; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

a 35.2% incidence rate of DVT in patients who undertook the lower extremity venous ultrasound examinations. Furthermore, the multivariate analyses showed that a high level of D-dimer, ICU admission, and without anticoagulant drugs were the risk factors of DVT.

Notably, the location of the vein thrombosis was primarily found in the distal lower extremity veins. In addition, all the patients who had proximal lower extremity vein thrombosis showed distal lower extremity vein thrombosis.

Deep vein thrombosis (DVT) is a predominant complication of critically ill hospitalized COVID-19 patients. It is one of the major possibly preventable causes of death. A recent study has reported a Padua Prediction Score of ≥ 4 in 40% hospitalized COVID-19 patients, implying that they were at high risk of developing DVT.[9] It has been reported that, the rate of DVT complications in critically ill COVID-19 patients was as high as 69%, although all the patients received prophylactic or therapeutic anticoagulation.[11] Elsewhere, the rate of DVT incident was 27% in ICU patients.[12] In current study, 35.2% of patients were diagnosed with DVT. The patients who undertook venous ultrasound examinations were selected by the treating
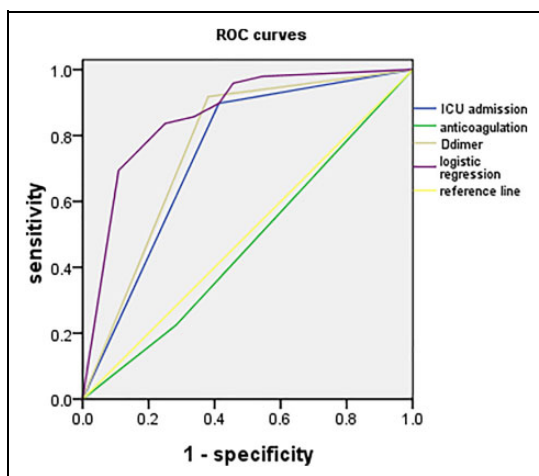
**Figure 1.** The ROC curve of DVT in patients with COVID-19 was predicted by risk factors and prediction probability. Abbreviations: COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; ICU, intensive care unit.

physician, this may overestimate the true rate of DVT. However, when we performed the venous ultrasound, all the patients were still in hospital, more DVT events may happened during the whole hospitalization. Although at least 70% of patients needed a serial examination, it was not always available due to limited medical resources.[13] Elsewhere, several reports has shown that only 1-6% patients who underwent the second examination were diagnosed with deep vein thrombosis.[14-16] In our study, all patients enrolled were Asian, and the incident of DVT was found to be lower compared to other studies that involved white and black people.[17,18]

The risk factors of DVT may transiently or persistently increase the risk of venous thromboembolism by inducing hypercoagulability, stasis, vascular wall damage or dysfunction.[19] Besides, immobilization and cancer are risk factors for comorbidities. However, comorbidity was not associated with DVT as a risk factor in our study.

We also noted that there were more patients in ICU in the DVT group compared to non-DVT. Similarly, the vital signs and laboratory tests worsen in the same group. Previous reports have revealed that patients with COVID-19 can rapidly develop critical diseases, causing a high inflammatory response, renal failure, respiratory failure, and liver dysfunction.[20] This may lead to an increased risk of DVT. Notably, patients at high risk of DVT have been shown to have a higher chance of admission to the ICU.[9] However, in this study, the mechanisms leading to DVT among COVID-19 patients in ICU may be different. Therefore, detailed studies on the mechanisms involved are indispensable.

Moreover, there was a strong association between high D-dimer levels and DVT. This may have been attributed to a systemic inflammatory response syndrome for activation of blood coagulation, detected as high fibrinogen. Also, COVID-19 patients with respiratory failure showed a high level of fibrinogen and D-dimer as an indicator of hypercoagulability.[21] Since clinical features cannot assess the diagnosis of DVT, the D-dimer testing may be used coupled with other assessments.[22] For patients at low risk of DVT, the diagnosis can be safely excluded if the D-dimer levels are normal.[23] On the other hand, as patients at high risk of DVT by clinical decision rule, the negative predictive value of D-dimer should be reduced, and the ultrasound examinations are necessary.[24,25]

Prophylactic anticoagulation drugs such as heparin and low molecular weight heparin have been reported to significantly reduce the risk of DVT in hospitalized COVID-19 patients.[26,27] However, despite anticoagulation usage, a high number of critically ill patients with COVID-19 developed DVT.[28] Here, there was no significant difference in the anticoagulant ratio between DVT and non-DVT groups before ultrasound examinations. However, the multivariate analyses revealed that the failure of the use of anticoagulant drugs was a risk factor of DVT. Nevertheless, the DVT group recorded higher ICU patients with less anticoagulant than non-DVT.

Some limitations of this study were worth noting. First, the patients were not enrolled consecutively or randomly but decided by their physician in charge. Moreover, a high proportion of critically ill patients were enrolled. The study might have overestimated the incidence of DVT in patients with COVID-19. Secondly, the examinations for the coagulable status were not performed comprehensively. For instance, it was found that some DVTs were due to other risk factors. Therefore, we recommend further research based on detailed mechanisms involved in the DVTs caused by the SARS-CoV-2.

In conclusion, this study demonstrates that coronavirus disease 2019 (COVID-19) is associated with a high incidence of deep vein thrombosis (DVT). Particularly, in critically ill patients with high D-dimer levels, and no anticoagulation was used. We also present the clinical features of DVT and non-DVT patients, which may help in the prevention and treatment of DVT.

## Availability of data and material

After publication, the data will be made available to others upon reasonable requests to the corresponding author. A proposal with a detailed description of study objectives and a statistical analysis plan will be needed for the evaluation of the requests. Additional materials might also be required during the process of evaluation. The de-identified participant data will be provided after approval from the corresponding author and Wuhan Jin Yin-tan Hospital.

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