Deep vein thrombosis in noncritically ill patients with coronavirus disease 2019 pneumonia: deep vein thrombosis in nonintensive care unit patients

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ABSTRACT

Background: Venous thromboembolic events have been one of the main causes of mortality among hospitalized patients with coronavirus disease 2019 (COVID-19) pneumonia. The aim of our study was to describe the prevalence of deep vein thrombosis (DVT) in noncritically ill patients with COVID-19 pneumonia and correlate such observations with the thromboprophylaxis received.

Methods: We performed a prospective cohort study of 67 patients admitted to the hospital for COVID-19 pneumonia. The diagnosis was confirmed using polymerase chain reaction testing of nasopharyngeal specimens. The deep veins were examined using compression duplex ultrasonography with the transducer on B-mode. The patients were separated into two groups for statistical analysis: those receiving low-molecular-weight heparin prophylaxis and those receiving intermediate or complete anticoagulation treatment. Risk analysis and logistic regression were performed.

Results: Of the 67 patients, 57 were included in the present study after applying the inclusion and exclusion criteria; 49.1% were women, and the patient mean age was 71.3 years. All 57 patients had undergone compression duplex ultrasonography. Of these 57 patients, 6 were diagnosed with DVT, for an in-hospital rate of DVT in patients with COVID-19 pneumonia of 10.5%. All the patients who had presented with DVT had been receiving low-molecular-weight heparin prophylaxis. The patients receiving prophylactic anticoagulation treatment had a greater risk of DVT (16.21%; 95% confidence interval, 0.04-0.28; $P = .056$) compared with those receiving intermediate or complete anticoagulation treatment. We also found a protective factor for DVT in the intermediate or complete anticoagulation treatment group (odds ratio, 0.19; 95% confidence interval, 0.08-0.46; $P < .05$).

Conclusions: Noncritically ill, hospitalized patients with COVID-19 pneumonia have a high risk of DVT despite receipt of correct, standard thromboprophylaxis. (J Vasc Surg Venous Lymphat Disord 2021;9:592-6.)

Keywords: COVID-19 pneumonia; Deep vein thrombosis; Thromboprophylaxis

After the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), healthcare systems around the world have unified resources and knowledge to contain the spread of the virus. Although coronaviruses have been well studied, SARS-CoV-2 has been reported to have particular characteristics that distinguish it from other viruses of the same family. Compared with severe acute respiratory syndrome coronavirus, SARS-CoV-2 has had a lower mortality rate. However, its ability to infect human hosts appears to be greater and the incubation period longer.[1] During infection, the plasma levels of proinflammatory and prothrombotic cytokines such as C-reactive protein, interleukin (IL)-6, IL-8, and D-dimer might have a role in the physiopathology of coronavirus disease 2019 (COVID-19)—induced SARS. Some studies have reported high levels of those cytokines, especially in patients with a more serious condition.[2]

One main complication reported to develop in hospitalized patients with COVID-19 has been venous thromboembolic events. In general, venous thromboembolic events are one of the main causes of mortality among hospitalized patients.[2] Diagnostic algorithms rely on clinical history, physical examination findings, and previous diseases to assess clinical probability scales. Compression duplex ultrasonography (CDUS) and computed tomography angiography are the reference standard diagnostic tools for evaluating deep vein thrombosis (DVT) and pulmonary embolism (PE).[3,4] Because 20% of patients admitted to intensive care units (ICUs) will experience a thromboembolic event,[5] numerous diagnostic

algorithms have been reported in the medical literature, albeit without any worldwide consensus reached.[6-8]

The incidence of PE has been reported for critically ill patients with COVID-19 pneumonia[5] and in a retrospective analysis by Chen et al.[9] In the latter study, the investigators reported that 25 of 1008 patients with COVID-19 had presented with PE.[9] Similarly, few data regarding the prevalence of DVT in hospitalized patients in noncritical care conditions with COVID-19 have been reported. Only 2 studies have recently reported an incidence of asymptomatic infrapopliteal DVT of 5.6% to 14.1% in patients in common wards.[10,11]

Therefore, we have described the prevalence of DVT among noncritically ill, hospitalized patients with COVID-19 pneumonia and correlated the findings with the thromboprophylaxis the patients received.

METHODS

We performed a prospective cohort study of 67 patients who had been admitted to our hospital because of COVID-19 pneumonia during April 2020. The diagnosis of COVID-19 was confirmed using polymerase chain reaction testing of nasopharyngeal specimens.

All the patients were assessed clinically by a vascular surgeon, and the Wells score was calculated. The inclusion criteria were as follows: the presence of COVID-19 pneumonia, presentation to the emergency department, and hospitalization required. The exclusion criteria were as follows: (1) palliative treatment, (2) pregnancy, (3) diagnosis of a thromboembolic event before hospital admission, (4) ICU treatment required, and (5) patient refusal to participate in the present study.

The demographic data recorded included cardiovascular risk factors (eg, dyslipidemia, hypertension, diabetes mellitus, smoking), chronic pulmonary or cardiac diseases (eg, chronic pulmonary obstructive disease, chronic ischemia heart disease, atrial fibrillation), the need for oxygen therapy, and the need for corticosteroid therapy (1 mg/kg of intravenous methylprednisolone administered every 24 hours). We also analyze the presence of sepsis using the diagnostic criteria of the Sepsis-3 International Consensus.[12] We used the Barthel Index as an observer-based instrument to measure the patients' physical function.[13]

Regardless of the symptoms and Wells score, all the patients had undergone bilateral CDUS, including the femoral, popliteal, calf, peroneal and tibial veins. Lower limb venous CDUS was performed using a Philips Epiq 5 scanner (Phillips HealthCare NV, Amsterdam, The Netherlands). A 5- to 10-MHz transducer was used for the infrainguinal area and a 3.5-MHz transducer was used for the abdominal vessels. The deep veins were examined using compression with the transducer on B-mode at 2-cm intervals.

Color Doppler flow was used to detect luminal filling defects, and Doppler tracings were obtained to detect

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, prospective, non-randomized cohort study
- **Key Findings:** Patients with coronavirus disease 2019 pneumonia treated with prophylactic, intermediate, or complete anticoagulation doses of low-molecular-weight heparin had a prevalence of lower extremity deep vein thrombosis (DVT) of 10.5%, with a cumulative incidence of 16.2% for those receiving a prophylactic dosage. We found a protective factor against DVT for patients receiving intermediate or complete anticoagulation treatment.
- **Take Home Message:** Noncritically ill patients with coronavirus disease 2019 pneumonia have a high risk of lower limb DVT despite correct prophylactic treatment.

spontaneous flow and phasicity. The diagnosis was established using the following ultrasound criteria: (1) no collapse or partial collapse of the vein lumen with transducer compression; (2) thrombus visualization within the vein lumen; (3) the absence of spontaneous venous flow; (4) the absence of a Doppler signal; and (5) an increase in vein diameter. At least two of these criteria were required for DVT to be diagnosed. We performed extended CDUS (including the infrapopliteal veins). Limited protocols required that a second study was performed within 5 to 7 days to safely exclude DVT.[14]

We collected the laboratory tests to obtain the D-dimer and IL-6 values. The D-dimer levels were obtained using the ACL TOP-500 (Instrumentation Laboratory, Bedford, Mass), with D-dimer high sensitivity as the reagent. A positive D-dimer level was set at 250 μg/L D-dimer units. The IL-6 levels were analyzed using a Cobas 8000 modular analyzer (Roche Diagnostics International AG, Risch-Rotkreuz, Switzerland).

DVT prophylaxis was assessed according to our hospital's protocol. Patients requiring anticoagulation therapy received low-molecular-weight heparin (LMWH) at different dosages. Those with an underlying disease (eg, atrial fibrillation; a prosthetic heart valve) had received LMWH at the complete anticoagulation dosage (1.5 mg/kg of enoxaparin every 24 hours). Those at high risk (eg, body mass index >30 kg/m^2, thrombophilia, a history of thromboembolic disease, active cancer) had received LMWH at an intermediate dosage (0.5 mg/kg of enoxaparin every 12 hours). The remaining patients had received LMWH at a prophylactic dosage (40 mg of enoxaparin every 24 hours). Bleeding complications were recorded and categorized according to a consensus report from the Bleeding Academic Research Consortium.[15]

Categorical variables are presented as frequencies and percentages. Normally distributed continuous variables are presented as the mean ± standard deviation.

Non-normally distributed continuous variables are presented as the median and interquartile range.

The patients were divided into two groups for statistical analysis: those who had received LMWH prophylaxis and those who had received intermediate or complete anticoagulation treatment. We performed a risk analysis and logistic regression test. Differences between the two groups were assessed using the χ^2 test (Yates correction) and the Student t test, as appropriate. Statistical significance was considered present for P values <.05.

The investigation ethics committee of Bellvitge University Hospital approved the present study (reference no. PR153/20). The study was performed in accordance with the 2013 Declaration of Helsinki consensus. All patient data were treated in accordance with the General Data Protection Regulations and Spanish Organic Law 15/1999 of December 13 on Protection of Personal Data and Royal Decree 1720/2007. All data were codified using a numeric code anonymously established for the purposes of the present study. All the patients were properly informed and provided written informed consent. The investigation data were saved in an electronic directory with restricted access supervised by the information system department of Bellvitge University Hospital. Statistical analyses were performed using R, version 3.4.0, software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Our study population included 67 patients admitted to the hospital with unilateral or bilateral pneumonia caused by COVID-19 during April 2020. Of the 67 patients, 10 were excluded from the present study in accordance with the inclusion and exclusion criteria. Of the 10 patients, 3 had refused to participate, 3 had received palliative treatment, and 4 had had a diagnosis of a thromboembolic event before hospital admission (3 had presented with DVT and PE and 1 with popliteal DVT). Thus, 57 patients were finally included, including 28 women (49.1%) and 29 men (50.9%). The mean age of the 57 patients was 71.3 ± 12.7 years. All included patients had undergone CDUS within a median of 9 days of hospitalization (interquartile range, 6-15 days). The baseline characteristics of our sample are presented in Table.

The clinical pretest probability of venous thromboembolism determined using the Wells score was unlikely for 98.2% of the patients and likely for 1.8% of patients. Of the 57 patients, 6 were diagnosed with DVT. Thus, the prevalence of in-hospital DVT in the patients with COVID-19 pneumonia was 10.5%. Of the six patients with DVT, five had had an unlikely Wells score and one had had a likely Wells score. All the patients had received LMWH treatment. However, different dosages had been administered in accordance with the hospital protocol: 64.9% had received a prophylactic dosage; 21.1%, intermediate

Table. Baseline characteristics

Characteristic	No. (%)
Barthel index	
100	33 (57.9)
60-95	10 (17.5)
45-55	4 (7)
20-35	3 (5.3)
<20	7 (12.3)
Risk factors	
Hypertension	42 (73.7)
Dyslipidemia	34 (59.6)
Diabetes mellitus	18 (31.6)
Smoking	9 (15.8)
COPD	8 (14)
Chronic ischemia heart disease or atrial fibrillation	18 (31.6)
Oxygen therapy	
FiO_2, 21%	19 (33.3)
NC	20 (35.1)
SFM (FiO_2, 26%)	3 (5.3)
SFM (FiO_2, 35%)	9 (15.8)
SFM (FiO_2, 50%)	2 (3.5)
Non-rebreather face mask (FiO_2, 100%)	4 (7)

COPD, Chronic obstructive pulmonary disease; *FiO2,* fraction of inspired oxygen; *NC,* nasal cannula; *SFM,* simple face mask.

anticoagulation treatment; and 14%, complete anticoagulation treatment because of an underlying disease.

All six of our patients had experienced asymptomatic DVT, except for one patient who had mentioned pain in the calf region and had had a swollen leg in the previous 24 hours. The most common area affected was distal (83.3%), and one patient had presented with femoropopliteal DVT (16.7%). All venous thromboembolic events had occurred in patients receiving a prophylactic dosage of LMWH. No such events were observed in the patients receiving intermediate or complete anticoagulation dosages. Only one patient with DVT had presented with worsening of respiratory symptoms and no thromboembolism. That patient had required ICU care. The remaining patients did not experience worsening of symptoms from COVID-19 infection.

All patients diagnosed with DVT were treated with LMWH at anticoagulation dosages during hospitalization. The patients were then switched to oral anticoagulation treatment during ambulatory follow-up for ≥3 months.

When analyzing the risk, we found a risk difference of 16.21% (95% confidence interval, 0.04%-0.28%) for patients receiving LMWH prophylaxis vs intermediate or complete anticoagulation treatment. However, the

difference was not statistically significant ($P = .056$). Logistic regression was performed, which revealed an odds ratio of 0.19 (95% confidence interval, 0.08-0.46; $P < .05$) for the intermediate or complete anticoagulation treatment group.

Corticosteroid treatment was used for 25 patients (43%). The incidence of DVT was 12% for the patients receiving corticosteroid treatment and 9.3% for the patients not receiving corticosteroid treatment. No statistically significant difference was found between the two groups ($P = .74$). Sepsis developed in 19 patients (33%). We found a tendency for more cases of DVT in the patients with sepsis (21%) compared with the patients without sepsis (5.2%; $P = .067$).

We found that the mean D-dimer levels were 467 ± 189 ng/mL in the patients without DVT and 576 ± 570 ng/mL in the patients with DVT ($P = .64$). Patients with DVT had had a mean IL-6 level of 12.8 ± 11.8 pg/mL. The patients without DVT had had a mean IL-6 level of 15.2 ± 13.9 pg/mL ($P = .69$).

Bleeding complications had developed in 1 patient in the intermediate or complete anticoagulation group (5%). No differences were observed between the two groups ($P = .22$).

DISCUSSION

We found that noncritically ill patients with COVID-19 pneumonia have a high risk of DVT during hospital admission despite receiving standard-dose thromboprophylaxis. Venous thromboembolic disease has been reported as one of the major complications occurring in patients with COVID-19.[9] Data reported from the initial autopsies shows that nonsuspected PE or DVT could account for 58% of deaths and for 33% was the main cause of death.[16] Nonetheless, it is not clearly known whether venous thromboembolic events were the main cause of clinical worsening and death among hospitalized patients or had been complications induced by the severe pneumonia and inflammatory responses. Therefore, we believe our efforts should also focus on the noncritically ill, hospitalized population to prevent the thromboembolic complications, which have been the most common events.

To the best of our knowledge, our study is one of the first to analyze asymptomatic DVT in a non-ICU setting. Even with correct, standard prophylaxis with LMWH, a DVT prevalence of 10.5% was observed in our study. Although one of our patients had developed femoropopliteal DVT, the remaining five patients had had infrapopliteal DVT. Management of infrapopliteal DVT remains under discussion; however, previously reported data of a standard population demonstrated a proximal progression rate of 15.5%.[17] We believe that infrapopliteal DVT should be treated, because a procoagulant state exists in patients with COVID-19 that has not been studied and could lead to higher progression rates.

The high proportion of patients with DVT can be explained by dysregulation of the coagulation system, which has been observed in patients with COVID-19 pneumonia. A recent study by Panigada et al[18] investigated the inflammatory response occurring secondary to COVID-19 by measuring blood from ICU-admitted patients using thromboelastography. Their findings highlighted that, more than the occurrence of an acute disseminated intravascular coagulation (with a low platelet count, low fibrinogen clotting activity, and high fibrin degradation products), the inflammatory response leads to a hypercoagulable state with high levels of fibrinogen, D-dimer, C-reactive protein, VIII factor, von Willebrand factor, low levels of antithrombin, and normal platelet counts, prothrombin time, and activated partial thromboplastin time.[18] A high procoagulant state, in addition to sepsis and medical treatment (eg, corticosteroid therapy) might be the reason patients with COVID-19 pneumonia have a greater risk of thromboembolic events compared with a standard hospitalized population.

Anticoagulation protocols have been reported by many societies, such as the International Society on Thrombosis and Hemostasis, North American Thrombosis Forum, European Society of Vascular Medicine, and International Union of Angiology, in which the standard prophylaxis dosage has been recommended as LMWH once daily.[6]

Also, our team observed a clear tendency toward a greater cumulative incidence of 16.2% for patients treated with LMWH at the prophylactic dosage compared with the incidence for those patients receiving intermediate or complete anticoagulation dosages. Additionally, the logistic regression model demonstrated that a protective factor against DVT was the use of intermediate or complete anticoagulation treatment. In addition, a recent study by Paranjpe et al[19] found that in a cohort of 2773 hospitalized patients with COVID-19, in-hospital survival was greater for the patients receiving anticoagulation therapy compared with the survival of those who had not received such therapy. Similarly, our results support those reported by Middeldorp et al[10] and Demelo-Rodriguez et al,[11] demonstrating a high incidence of DVT in noncritically ill patients with COVID-19.

The results from an autopsy study suggested that the inflammatory response might have caused in situ immunothrombosis in the microcirculation of the lungs.[20] A separate study reported by van Dam et al[21] concluded that the phenotype of pulmonary embolism in patients with COVID-19 might differ from that for patients without COVID-19 pneumonia. The investigators suggested that in situ immunothrombosis was the main cause. However, despite the sample size, the main limitation of their study was that the patients had not undergone lower limb CDUS.[21]

Our study group believes that the physiopathological findings notwithstanding, selected patients could benefit from intermediate anticoagulation dosages and avoid experiencing a thromboembolic event because six of our patients, despite receiving standard prophylaxis, had developed DVT. These findings and results are noteworthy, because they lead to the question of whether standard prophylaxis treatments will be sufficient and whether treatment to prevent DVT should be more aggressive in patients with COVID-19 pneumonia. Clinically randomized trials are required to best address these questions to improve clinical practice and provide better patient care.

The present study had only two main limitations. First, because the sample size was small, the potential for statistically significant results was low. Second, the specific COVID-19 treatments changed weekly owing to the rapid advances occurring concerning COVID-19 during the pandemic. Thus, external validity could have been affected.

CONCLUSIONS

Noncritically ill patients admitted to the hospital because of COVID-19 pneumonia have a high risk of DVT despite receipt of correct, standard thromboprophylaxis.

AUTHOR CONTRIBUTIONS

Conception and design: XJ, MH, AR, AI, AS, RV
Analysis and interpretation: XJ, MH, AR, AI, AS, RV
Data collection: XJ, MH, AR
Writing the article: XJ, MH, AR
Critical revision of the article: XJ, MH, AR, AI, AS, RV
Final approval of the article: XJ, MH, AR, AI, AS, RV
Statistical analysis: XJ, MH, AR, AI
Obtained funding: XJ, MH, AR, AI
Overall responsibility: XJ

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