Differences Between Surviving and Non-surviving Venous Thromboembolism COVID-19 Patients: A Systematic Review

Mauricio Castillo-Perez
    TecSalud: Instituto Tecnologico y de Estudios Superiores de Monterrey Escuela de Medicina Ignacio A Santos

Carlos Jerjes-Sanchez ( jerjes@prodigy.net.mx )
    Centro de Investigacion Biomedica del Hospital Zambrano Hellion, TecSalud. Instituto de Cardiologia y Medicina Vascular, TecSalud  https://orcid.org/0000-0003-3222-7405

Alejandra Castro-Varela
    TecSalud: Instituto Tecnologico y de Estudios Superiores de Monterrey Escuela de Medicina Ignacio A Santos

Jose Gildardo Paredes-Vazquez
    Hospital Zambrano Hellion Instituto de Cardiologia y Medicina Vascular

Eduardo Vazquez-Garza
    TecSalud: Instituto Tecnologico y de Estudios Superiores de Monterrey Escuela de Medicina Ignacio A Santos

Ray Erick Ramos-Cazares
    TecSalud: Instituto Tecnologico y de Estudios Superiores de Monterrey Escuela de Medicina Ignacio A Santos

Jose Alfredo Salinas-Casanova
    TecSalud: Instituto Tecnologico y de Estudios Superiores de Monterrey Escuela de Medicina Ignacio A Santos

Abigail Montserrat Molina-Rodriguez
    TecSalud: Instituto Tecnologico y de Estudios Superiores de Monterrey Escuela de Medicina Ignacio A Santos

Arturo Adrian Martinez-Ibarra
    TecSalud: Instituto Tecnologico y de Estudios Superiores de Monterrey Escuela de Medicina Ignacio A Santos

Mario Alejandro Fabiani
    TecSalud: Instituto Tecnologico y de Estudios Superiores de Monterrey Escuela de Medicina Ignacio A Santos

Yoezer Z Flores-Sayavedra
Research

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Abstract

Background: Systematic reviews of venous thromboembolism COVID-19 patients focus on the incidence, primary and secondary venous thromboembolism prevention, bleeding complications, and the association of D-dimer with mortality. We analyzed therapeutic approaches, outcomes, clinical presentation, risk stratification, and patient characteristics that survived and did not survive.

Methods: We searched for systematic reviews, cohorts, case series, case reports, editor letters, and venous thromboembolism COVID-19 patients’ abstracts following PRISMA and PROSPERO statements. The objective was to assess therapeutic trends and clinical outcomes of venous thromboembolism COVID-19 patients. Inclusion: COVID-19 patients with venous thromboembolism confirmed by an imaging method (venous doppler ultrasound, ventilation-perfusion lung scan, computed tomography pulmonary angiogram, pulmonary angiography). We assessed the original Pulmonary Embolism Severity Index in two groups, survivors and those who died. We defined major bleedings according to the International Society of Thrombosis and Haemostasis criteria.

Results: We performed a systematic review from August 9 to August 30, 2020. We collected 1,535 papers from PubMed, Scopus, Web of Science, Wiley, and Opengrey. We extracted data from 89 studies. Unfractionated and low-molecular-weight heparin drove parenteral anticoagulation. The Food and Drug Administration-approved alteplase regimen guided the advanced treatment in both groups. The mortality was high (21.6%), with a low incidence of bleeding complications in those who survived: Pulmonary Embolism Severity Index class II and III identified patients who lived. Patients who experienced venous thromboembolism events at home were more likely to live than in-hospital events. Patients who died had a higher D dimer expression and right ventricular dysfunction.

Conclusions: We determined a high mortality incidence of pulmonary embolism (21.6%) related to hypertension, an increased inflammatory response, prothrombotic state, severe COVID-19, massive pulmonary embolism, intensive care unit admission, low venous thromboembolism prophylaxis, and bleeding complications. The original Pulmonary Embolism Severity Index could be helpful in the risk stratification. Overlapping severe COVID-19 pneumonia and pulmonary embolism is a challenge.

Background

The rapidly evolving coronavirus disease 2019 (COVID-19) global pandemic is one of the most significant public health challenges since the Spanish flu pandemic over 100 years ago (1). COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a multifaceted disease characterized by a wide range of clinical presentations and degrees of severity (2). In the beginning, the target organ seemed to be only the respiratory system, inducing severe pneumonia and acute respiratory distress syndrome. However, an important lesson learned was that SARS-CoV-2 causes a high prothrombotic state, venous, and arterial thrombosis (1). The clinical presentation eventually resembles a thrombotic storm observed in vasculitis, disseminated intravascular coagulation, heparin-induced thrombocytopenia,
and thrombophilia (3). Additionally, thrombosis mechanisms linking inflammation pathways, endothelial activation, coagulation system activity, immunothrombosis, cytokine storm, and renin-angiotensin-aldosterone system dysregulation (4–8) seem to be involved.

Therefore, in severe COVID-19, venous thromboembolism (VTE) emerges as a critical and frequent complication (9, 10), with a high incidence (15.3%) and mortality rate (45.1%), in pulmonary embolism (PE) patients (11). Although there is a trend to better survival in patients treated with heparins (anticoagulation and anti-inflammatory effect) (12, 13), we do not have enough data on the best primary prevention doses, therapeutic approaches, and outcomes (9, 14, 15). Also, there are no advanced treatment recommendations in massive and submassive PE (16, 17). Therefore, we performed a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement to determine the therapeutic trends and outcomes in VTE COVID-19 patients. Also, we assessed the original Pulmonary Embolism Severity Index (PESI) in PE patients.

**Methods**

**Search strategy**

We searched for systematic reviews, cohorts, case series, case reports, editor letters, and VTE COVID-19 patients' abstracts through the PRISMA statement search (18). We register the protocol in the International Prospective Register protocol of Systematic Reviews (PROSPERO); registration number: CRD42020203688). The patients must have received anticoagulation or thrombolysis. The objective was to assess the therapeutic trends and clinical outcomes of VTE COVID-19 patients.

Additionally, we analyzed the clinical presentation, risk stratification, and diagnostic approach. We included deep vein thrombosis (DVT) and PE confirmed by an imaging method (venous doppler US, ventilation-perfusion lung scan, computed tomography pulmonary angiogram, pulmonary angiography). We assessed the original PESI since it works better than the simplified PESI (19). We established two groups, survivors and those who died. We performed a systematic review through PubMed, Scopus, Web of Science, Wiley, and OpenGrey and provided the complete search strategies in the e-Appendix. We used the snowballing method (20), a manual search to avoid lost reports, controlled vocabulary, and no language restriction. We do not contact authors to obtain additional information in cases with critical missing variables.

**Study selection and data collection**

We identified potentially eligible studies by examining titles and abstracts. We obtained full papers to assess eligibility criteria before the critical appraisal and extracted cases that met the eligibility criteria. All investigators analyzed data extraction of every case report to improve quality data extraction. The corresponding author is a cardiologist with expertise in the field (CJS). We conducted a group discussion daily to assess all the information extracted from the cases included in a database. Disagreements were solved posteriorly by consensus. We performed two meetings to ensure the data's quality through a
random review of 20% of the papers. The primary outcomes were the therapeutic approaches, in-hospital death, intracranial hemorrhage (ICH), major bleeding, and minor bleedings.

Additionally, we analyzed the clinical presentation, the PE risk, COVID-19 severity, VTE primary prevention, and the thrombus's location in the pulmonary circulation. According to the International Society of Thrombosis and Haemostasis criteria, we defined major bleedings (21); we established the presence of right ventricular dysfunction according to the European Society of Cardiology guidelines of PE: right ventricular end-diastolic diameter/left ventricular end-diastolic diameter ratio ≥ 2:1, (b) regional or global right ventricular hypokinesis, (c) McConnell’s sign, (d) right ventricular diameter > 35 mm, (e) systolic pulmonary arterial pressure ≥ 50 mm Hg; B-type brain natriuretic peptide (BNP) measurement (> 90 pg/mL) or N-terminal proBNP (NT-proBNP) (> 300 pg/mL)²; dynamic electrocardiographic changes (new complete or incomplete right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion) (22); other definitions, including the PESI score, massive PE and intensive care unit (ICU) VTE risk factors, are available in the e-Appendix.

**Exploratory analysis**

Based on the high SARS-CoV-2 thrombogenicity and to understand its behavior in the venous system, we also analyzed acute cerebral vein thrombosis (CVT) associated or not with VTE.

**Statistical analysis**

We used summary statistics for continuous and categorical variables according to their types and distributions. We report the frequency and percentage (n > 20) for categorical variables, and for continuous variables, we report the median and standard deviation. We used the IBM SPSS® software platform for advanced statistical analysis.

**Results**

We carried out the systematic review from August 9 to August 30, 2020. Figure 1 shows the flowchart, including the four phases of PRISMA, and we obtained, eliminated, and excluded duplicated reports. In the identification phase, we collected 1,535 papers from PubMed, Scopus, Web of Science, Wiley, and Opengrey. We carefully reviewed the full text for eligibility criteria and selected 107 reports for the quality assessment. Finally, we extracted the data for this review from 89 studies.

**Baseline demographics and primary outcomes**

Table 1 shows baseline characteristics, VTE classification, PE risk stratification, therapeutic trends, and survival and death patients' outcomes. We identified 143 COVID-19 patients with VTE; most were relatively young overweight males with isolated PE with or without proximal DVT. The proportion of low-risk and submassive PE was higher in patients who survived than those who died, where massive PE was predominant (Table 1). In this group, the detection of proximal or distal DVT was scarce. Unfractionated
and low-molecular-weight heparin drove parenteral anticoagulation in both groups. Also, direct-acting oral anticoagulant use was rare. The Food and Drug Administration-approved alteplase regimen drove the advanced treatment in both groups (Table 1). The mortality was high (21.6%), and there was a low incidence of bleeding complications, including ICH, in those who survived (Table 1). Table 2 shows the key findings related to medical history, patient and in-hospital risk factors, clinical presentation, PESI, and the setting of symptoms onset. Among the usual comorbidities in COVID-19, hypertension had a higher incidence in patients who died. The most prevalent VTE risk factors had a relationship with in-hospital and ICU stays in patients who died (Table 2). The earliest clinical PE findings were severe oxygen desaturation and sudden dyspnea, and leg pain in DVT survived patients (Table 2). A remarkable characteristic was the lowest oxygen saturation in those who died. The original PESI class II and III identified patients who lived (Table 2). Finally, patients with acute VTE events at home were more likely to live than in-hospital events.
Table 1
Baseline demographics, VTE classification, risk stratification, therapeutic approaches and outcomes

| Variables                  | All Patients | Survival | Death |
|----------------------------|--------------|----------|-------|
|                            | N = 143 (%)  | N = 112 (%) | N = 31 (%) |
| Age (years), mean ± SD     | 58.5 ± 12.7  | 58.1 ± 13.6 | 60.0 ± 8.8 |
| Gender (male)              | 91 (63.6)    | 70 (62.5)  | 21 (67.7) |
| BMI (kg/m²), mean ± SD     | 30.9 ± 5.6   | 30.3 ± 5.6 | 31.6 ± 5.6 |
| VTE classification         |              |          |       |
| Isolated pulmonary embolism| 112 (78.3)   | 85 (75.9) | 27 (87.1) |
| Isolated deep venous thrombosis| 12 (8.4) | 10 (8.9) | 2 (6.5) |
| Pulmonary embolism plus DVT| 18 (12.6)   | 16 (14.3) | 2 (6.5) |
| Pulmonary embolism plus CVT| 1 (0.7)     | 1 (0.9)   | 0 (0) |
| PE risk stratification (ACC/AHA) |          |          |       |
| Low risk                   | 24 (18.3)    | 23 (20.5) | 1 (3.2) |
| Submassive                 | 31 (23.7)    | 29 (25.9) | 2 (6.5) |
| Massive                    | 39 (29.8)    | 21 (18.8) | 18 (58) |
| Unable to classify         | 37 (28.2)    | 29 (25.9) | 8 (25.8) |
| DVT classification         |              |          |       |
| Proximal DVT               | 14 (9.8)     | 11 (9.8)  | 3 (9.7) |
| Distal DVT                 | 5 (3.5)      | 5 (4.5)   | 0 (0)  |
| Proximal plus distal DVT   | 5 (3.5)      | 5 (4.5)   | 0 (0)  |
| Upper limb DVT             | 6 (4.2)      | 4 (3.6)   | 2 (6.5) |
| Treatment                  |              |          |       |
| Unfractionated heparin     | 28 (19.6)    | 22 (19.6) | 6 (19.4) |
| Low-molecular-weight-heparin| 57 (39.9)   | 49 (43.8) | 8 (25.8) |
| Warfarin                   | 0 (0)        | 0 (0)     | 0 (0)  |
| Fondaparinux               | 3 (2.1)      | 3 (2.7)   | 0 (0)  |
| Direct oral anticoagulants | 8 (5.6)      | 8 (7.1)   | 0 (0)  |

VTE: venous thromboembolism; DVT: deep venous thrombosis; CVT: cerebral venous thrombosis; DOACs: direct-acting oral anticoagulants.
| Variables                      | All Patients  | Survival          | Death          |
|-------------------------------|---------------|-------------------|----------------|
|                               | N = 143 (%)   | N = 112 (%)       | N = 31 (%)     |
| Apixaban                      | 4 (2.8)       | 4 (3.6)           | 0 (0)          |
| Rivaroxaban                   | 2 (1.4)       | 2 (1.8)           | 0 (0)          |
| Unspecified DOACs             | 2 (1.4)       | 2 (1.8)           | 0 (0)          |
| Alteplase 100 mg              | 33 (23.1)     | 20 (17.9)         | 13 (41.9)      |
| Alteplase 50 mg               | 6 (4.2)       | 4 (3.6)           | 2 (6.5)        |
| Tenecteplase                  | 1 (0.7)       | 0 (0)             | 1 (3.2)        |
| CDT                           | 1 (0.7)       | 1 (0.9)           | 0 (0)          |
| USCDT                         | 3 (2.1)       | 3 (2.7)           | 0 (0)          |
| Mechanical thrombectomy       | 3 (2.1)       | 3 (2.7)           | 0 (0)          |
| Surgical thrombectomy         | 4 (2.8)       | 3 (2.7)           | 1 (3.2)        |
| **Outcomes**                  |               |                   |                |
| Death                         | 143 (100)     | 112 (78.39)       | 31 (21.6)      |
| Intracranial hemorrhage       | 2 (1.4)       | 1 (0.9)           | 1 (3.2)        |
| Major bleeding                | 2 (1.4)       | 1 (0.9)           | 1 (3.2)        |
| Minor bleeding                | 2 (1.4)       | 1 (0.9)           | 1 (3.2)        |

VTE: venous thromboembolism; DVT: deep venous thrombosis; CVT: cerebral venous thrombosis; DOACs: direct-acting oral anticoagulants.
Table 2
VTE risk factors, clinical presentation, PESI and onset

| Variables                                    | All patients N = 143 (%) | Survival N = 112 (%) | Death N = 31 (%) |
|----------------------------------------------|--------------------------|----------------------|------------------|
| **Medical history and risk factors**         |                          |                      |                  |
| Hypertension                                 | 50 (35)                  | 34 (30.4)            | 16 (51.6)        |
| Diabetes                                     | 33 (23.1)                | 25 (22.3)            | 8 (25.8)         |
| Lung disease                                 | 16 (11.2)                | 15 (13.4)            | 1 (3.2)          |
| Medical history of cancer                    | 7 (4.9)                  | 5 (4.5)              | 2 (6.5)          |
| Active cancer                                | 5 (3.5)                  | 3 (2.7)              | 2 (6.5)          |
| Previous venous thromboembolism              | 2 (1.4)                  | 2 (1.8)              | 0 (0)            |
| **In-hospital and ICU risk factors**         |                          |                      |                  |
| Immobilization                               | 88 (61.5)                | 63 (56.3)            | 25 (80.6)        |
| Sedation                                     | 51 (35.7)                | 27 (24.1)            | 24 (77.4)        |
| Central venous lines                         | 52 (36.4)                | 28 (25)              | 24 (77.4)        |
| Vasopressors                                 | 15 (10.5)                | 4 (3.6)              | 11 (35.5)        |
| **VTE Clinical presentation**                |                          |                      |                  |
| $O^2$ saturation (%), mean ± SD               | 87.9 ± 7.6               | 88.3 ± 7.4           | 85 ± 9.4         |
| Sudden dyspnea                               | 31 (21.7)                | 29 (25.9)            | 2 (6.5)          |
| Progressive dyspnea                           | 26 (18.2)                | 23 (20.5)            | 3 (9.7)          |
| Pleuritic chest pain                         | 20 (14)                  | 19 (17)              | 1 (3.2)          |
| Ischemic chest pain                          | 2 (1.4)                  | 2 (1.8)              | 0 (0)            |
| Leg pain                                     | 13 (9.1)                 | 11 (9.8)             | 2 (6.5)          |
| **Original PESI**                            |                          |                      |                  |
| I (Very low risk)                            | 13 (9.1)                 | 13 (11.6)            | 0 (0)            |
| II (Low risk)                                | 27 (18.9)                | 25 (22.3)            | 2 (6.5)          |
| III (Intermediate risk)                      | 45 (31.5)                | 37 (33)              | 8 (25.8)         |
| IV (High risk)                               | 11 (7.7)                 | 11 (9.8)             | 0 (0)            |
| V (Very high risk)                           | 35 (24.5)                | 19 (17)              | 16 (51.6)        |
| **VTE onset**                                |                          |                      |                  |
Table 3 shows the use of biomarkers and imaging studies in both groups. Patients who died had a higher D dimer expression and right ventricular dysfunction (Table 3). Biomarker use was even low guidelines recommendations (22) (Table 3). The computed tomography pulmonary angiography (CTPA) demonstrated a wide distribution of thrombus locations in surviving patients (Table 3). Table 4 shows the clinical presentation, laboratory, imaging findings, and primary prevention in COVID-19. The variables mainly related to mortality were acute respiratory distress syndrome, mechanical ventilation, ICU stay, and higher C reactive protein measurements in PE patients. We also identified reduced thromboprophylaxis use in both groups.

### Table 3
Biomarkers and imaging studies in venous thromboembolism COVID-19 patients

| Variables                        | All patients          | Survival          | Death            |
|----------------------------------|-----------------------|-------------------|------------------|
|                                  | N = 143 (%)           | N = 112 (%)       | N = 31 (%)       |
| Biomarkers                       |                       |                   |                  |
| D-dimer (mcg/mL), median (IQR)   | 7794 (3320–17460)     | 7700 (3200–16125) | 8897 (4352–33175) |
| Hs-cTn (ng/mL), median (IQR)     | 57 (14.5–191)         | -                 | -                |
| Ferritin (ng/mL), median (IQR)   | 765 (402–1456)        | -                 | -                |
| Imaging studies                  |                       |                   |                  |
| Right ventricular dysfunction (TTE) | 56 (39.2)            | 35 (31.3)         | 21 (67.8)        |
| CTPA                             |                       |                   |                  |
| Saddle PE                        | 10 (7)                | 9 (8)             | 1 (3.2)          |
| Main branches                    | 38 (26.6)             | 34 (30.4)         | 4 (12.9)         |
| Lobar branches                   | 22 (15.4)             | 19 (17)           | 3 (9.7)          |
| Segmental branches               | 27 (18.9)             | 23 (20.5)         | 4 (12.9)         |
| Subsegmental branches            | 7 (4.9)               | 7 (6.3)           | 0 (0)            |
| Doppler US and DVT               | 30 (20.9)             | 25 (22.3)         | 5 (16.1)         |
| Variables                                | All patients N = 143 (%) | Survival N = 112 (%) | Death N = 31 (%) |
|------------------------------------------|--------------------------|----------------------|------------------|
| **COVID-19 severity**                    |                          |                      |                  |
| Asymptomatic                             | 14 (9.8)                 | 12 (10.7)            | 2 (6.5)          |
| Mild symptoms                            | 9 (6.3)                  | 8 (7.1)              | 1 (3.2)          |
| Fever                                    | 27 (18.9)                | 23 (20.5)            | 4 (12.9)         |
| Pneumonia                                | 62 (43.4)                | 55 (49.1)            | 7 (22.6)         |
| ARDS                                     | 58 (40.6)                | 37 (33)              | 21 (67.7)        |
| Mechanical ventilation                   | 56 (39.2)                | 32 (28.6)            | 24 (77.4)        |
| ICU                                      | 69 (48.3)                | 40 (35.7)            | 29 (93.5)        |
| **Laboratories**                         |                          |                      |                  |
| Leukocytes ($10^9$ u/L), median (IQR)    | 11.9 (9.7–15.4)          | 11.4 (9.4–13.6)      | 13.8 (10.8–20.3) |
| Lymphocytes ($10^3$ u/L), mean ± SD      | 928.3 ± 448.5            | 994.1 ± 461.5        | 731.1 ± 360.1    |
| Platelets ($10^3$ u/L), mean ± SD        | 246.8 ± 129.8            | 254.4 ± 122.9        | 233.7 ± 143.7    |
| LDH (U/L), median (IQR)                  | 575 (391.8–739.3)        | -                    | -                |
| CRP (mg/L), median (IQR)                 | 113.1 (50.6–222.5)       | 92.9 (50–160)        | 244.9 (154–345.4)|
| RT-PCR SARS-CoV-2 (+)                    | 142 (99.3)               | 111 (99.1)           | 31 (100)         |
| **Imagen studies**                       |                          |                      |                  |
| Bilateral infiltrates (chest X-ray)       | 49 (34.3)                | 37 (33)              | 12 (38.7)        |
| CT with CO-RADS 5                        | 49 (34.3)                | 43 (38.4)            | 6 (19.4)         |
| **Thromboprophylaxis**                   |                          |                      |                  |
| Unfractionated heparin                   | 17 (11.9)                | 11 (9.8)             | 6 (19.4)         |
| Low-molecular weight heparin             | 31 (21.7)                | 20 (17.9)            | 11 (35.5)        |
| Unspecified                              | 3 (2.1)                  | 2 (1.8)              | 1 (3.2)          |
| Not received                             | 89 (62.2)                | 77 (68.8)            | 12 (38.7)        |
| **Previous anticoagulation treatment**   |                          |                      |                  |
| Direct-acting oral anticoagulants        | 1 (0.7)                  | 1 (0.9)              | 0 (0)            |
| Variables | All patients N = 143 (%) | Survival N = 112 (%) | Death N = 31 (%) |
|-----------|--------------------------|----------------------|------------------|
| VKA       | 2 (1.4)                  | 1 (0.9)              | 1 (3.2)          |

**Exploratory Analysis**

We identified 15 young patients with a similar gender proportion practically without a history of contraceptives (Table 5). CVT clinical presentation included neurologic alterations at home, abnormal D dimer measurements, and only one case associated with a submassive PE. Most patients were asymptomatic or had COVID-19 pneumonia. Despite in-hospital primary prevention, five patients had CVT. We identified a remarkably high prevalence of ICH (10/15 patients) and increased mortality (3/15 patients) (Table 5).
Table 5
Exploratory analysis: cerebral vein thrombosis

| Variables                              | N = 15 |
|----------------------------------------|--------|
| Age                                    | 56 ± 14.3 |
| Gender (male)                          | 7      |
| **Risk factors**                       |        |
| Comorbidities (≥ 1)                    | 2      |
| Oral contraceptives                    | 2      |
| D-dimer (mcg/mL), mean ± SD            | 3698.4 ± 2017.3 |
| Submassive pulmonary embolism          | 1      |
| **CVT presentation**                   |        |
| Altered mental status                  | 6      |
| Headache                               | 8      |
| Aphasia                                | 6      |
| Hemiparesis                            | 7      |
| Seizures                               | 4      |
| At home                                | 9      |
| **COVID-19 clinical presentation**     |        |
| Fever                                  | 3      |
| Progressive dyspnea                     | 3      |
| Asymptomatic                           | 3      |
| Mild symptoms                          | 1      |
| Pneumonia                              | 6      |
| CT with CO-RADS 5                      | 6      |
| Thromboprophylaxis                     | 5      |
| **Treatment and outcomes**             |        |
| Unfractionated heparin                 | 3      |
| Low-molecular-weight-heparin            | 12     |
| Intracranial hemorrhage                | 7      |
| Death                                  | 3      |
Discussion

This systematic review highlights the therapeutic trends and outcomes of VTE survivors compared with those who died. The main observations were: First, unfractionated and low-molecular-weight heparin was the cornerstone in the VTE treatment. Also, the Food and Drug Administration-approved systemic alteplase regimen drives advanced therapy in PE patients. Second, we identified high mortality in the ICU associated with severe COVID-19 with a low incidence of bleeding complications in massive PE. Third, the original PESI score II-III recognized patients who survived, suggesting its usefulness in the risk stratification in COVID-19 patients. Fourth, elevated C reactive protein and D dimer measurements and right ventricular dysfunction identified poor in-hospital outcomes. Finally, the exploratory analysis showed the same high ICH incidence in CVT mild COVID-19 patients than non-COVID-19 patients.

Recent systematic reviews and meta-analyses focused on the incidence, primary and secondary VTE prevention, bleeding complications (23–26), and the association of D-dimer with mortality (27, 28). Therefore, therapeutic approaches, outcomes, clinical presentation, risk stratification, and patient characteristics are not well defined.

Patients with severe COVID-19 disease are at high risk for thromboinflammation since they have SARS-CoV-2 infection, risk factors, cardiovascular, renal, or chronic pulmonary inflammatory comorbidities (2). An increased frequency of arterial and venous thrombosis at the beginning of the pandemic was remarkable (29). VTE is now recognized as among the predominant cardiovascular hazards (29), with the highest incidence in the intensive care unit setting (25%), increasing to 69% after surveillance venous ultrasonography (29). Also, thromboprophylaxis, the foundation to prevent in-hospital VTE, fails in a subset of COVID-19 patients (29). Additionally, quantifying the risk of thrombosis and cardiovascular complications is complicated in this heterogeneous population by reports of limited sample size, restriction of assessments to the ICU setting, outcome definitions, and differing thromboprophylaxis strategies (29).

Our findings suggest that intravenous or subcutaneous anticoagulation remains the cornerstone of therapy in deep venous thrombosis and PE COVID-19 patients. Strategies for reperfusion therapy included the thrombolysis regimen recommended for international guidelines (22) or "safe dose" in PE patients (30–32) (Table 1). The rationale for systemic fibrinolysis in PE is to avert or improve impending clinical instability secondary to right ventricular dysfunction to improve the outcome. Several pulmonary hypertension mechanisms (PE, hypoxic vasoconstriction, pulmonary microthrombi, ACE2 dysregulation, and cytokine storm) inducing right ventricular dysfunction demand a CTPA before clinical decision-making in this population (33). Despite systemic thrombolysis, bleeding complication incidence was lower (0.9% vs. 3.2%; Table 1) than recent evidence (21.4%) using intermediate- or full-heparin dose without advanced treatment and bleeding definitions according to the individual studies (26). This difference in the incidence of bleeding complications is unclear because relevant clinical or significant bleedings are usually reported. We showed high mortality (21.6%) in massive PE in SARS-CoV-2 infected individuals with severe COVID-19 (Table 1). However, it is lower than observed in massive PE non-COVID-
19 patients (33%) (34); the mortality rates observed are also related to severe COVID-19 and higher than previous other viral pandemics experienced in the past (35).

The original PESI score is a helpful tool for immediate and bedside risk stratification (22); whether this score helps COVID-19 patients is unanswered. The original PESI risk score had greater precision in identifying low and intermediate PE risks and identified a high proportion of high-risk patients with very high risk (19) (Table 2). Current COVID-19 restrictions delay or avoid all recommended diagnostic approaches in high clinical suspicion PE patients (22); thus, the original PESI score could be helpful in high clinical suspicion COVID-19 patients. Clinicians should also consider that the simplified PESI score may fail (36), and a multimodal approach use improves the accuracy of risk stratification. (PESI score definition is available in the e-Appendix).

The main characteristics of patients who died included hypertension, a high inflammatory, and prothrombotic state, severe COVID-19 associated with massive PE, ICU admission, and low use of VTE primary prevention (Tables 2, 3, and 4). Another remarkable finding shows VTE events despite thromboprophylaxis. Current evidence suggests administering heparin at standard doses in non-critically ill patients without risk factor for thrombosis or at a high dose for critically ill patients (intermediate or therapeutic dose) (37). Additionally, high dose thromboprophylaxis might be adjusted according to inflammation's progression without increasing bleeding risk in critically ill COVID-19 patients (38). Randomized controlled trials comparing different thromboprophylaxis doses are needed to establish the best therapeutic approach (38). The most consistent biomarker abnormalities related to mortality were higher C-reactive protein and D-dimer measurement levels, both associated with ICU admission and death (15). Patients with severe COVID-19 are at increased risk of thromboinflammation as they have pro-inflammatory risk factors, cardiopulmonary comorbidities related to inflammation, and cytokine storm (33). Additionally, there are several plausible reasons for elevated D-dimer in patients with SARS-CoV-2: severe infection, VTE, pulmonary and coronary microthrombus, acute kidney, cardiac injury, and pro-inflammatory cytokines (28).

Overlapping severe COVID-19 pneumonia and PE is a challenge, and any pneumonia increases the risk of VTE (33). A higher D-dimer measurement and severe oxygen desaturation are possible clinical markers to establish high clinical suspicion and PE severity. Recently, in a case series, the clinical presentation was similar: persistent or worsening respiratory symptoms increased oxygen requirements and DD levels that were several-fold higher (39). We suggest that physicians in charge should consider these clinical variables and never ignore abnormal or significantly elevated D-dimer because it is an expression of the coagulation system and secondary fibrinolysis activity, suggesting a high risk of acute thrombosis or, at least, VTE (33). Sudden hypotension could be another clinical element for PE suspicion in the setting of pneumonia COVID-19 (33).

We identified differences in the baseline characteristics reported previously in CVT patients (40–42). Only two patients had a history of oral contraceptives and no history of hereditary prothrombotic factors. These findings suggest an essential role of SARS-CoV-2 in pathogenicity as a trigger of thrombosis.
Although early ICH (present at the time of diagnosis) is a frequent complication (40%) (41, 42), current evidence demonstrates a low incidence of new ICH after initiating treatment with anticoagulation (40–43). This analysis identified a high ICH incidence (four early and six after treatment), secondary to a high pro-inflammatory state induced by SARS-CoV-2. Although anticoagulation is the standard of care in CVT patients (avoid thrombus growth, prevent VTE), the high prevalence of ICH suggests that physicians in charge have to be warning for early detection of this feared complication (42).

The significant limitations of the study included a potential loss of case reports from search engines. There is a trend not to report patients with poor in-hospital outcomes or serious adverse events. It was not possible to obtain information on the timing of the D-dimer measurements and other biomarkers. We got the most information from case reports, and we did not contact any author. As for any systematic review, our results should be considered hypothesis-generating; prospective studies are mandatory to confirm our findings.

**Conclusion**

In this systematic review analyzing 143 survivors and non-survivors VTE COVI-19 patients, we determined a high mortality incidence of PE (21.6%) related to hypertension, a high inflammatory, prothrombotic state, severe COVID-19, massive PE, ICU admission, and low VTE prophylaxis, and bleeding complications. Overlapping severe COVID-19 pneumonia and PE is a challenge. A higher D-dimer measurement and severe oxygen desaturation are possible clinical markers to establish a high-clinical suspicion and severity PE. The original PESI could be useful in risk stratification. Prospective clinical trials are mandatory to elucidate the optimal primary or secondary prevention and advanced treatment in this population of patients.

**Abbreviations**

coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); venous thromboembolism (VTE); pulmonary embolism (PE); original Pulmonary Embolism Severity Index (PESI); the International Prospective Register protocol of Systematic Reviews (PROSPERO); the Preferred Reporting Items for Systematic Reviews and Metanalyses (PRISMA); deep vein thrombosis (DVT); simplified Pulmonary Embolism Severity Index (PESI); B-type brain natriuretic peptide (BNP); N-terminal proBNP (NT-proBNP); cerebral vein thrombosis (CVT); intensive care unit (ICU); intracranial hemorrhage (ICH); computed tomography pulmonary angiography (CTPA)

**Declarations**

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MCP: Substantial contributions to the conception, design of the work; research idea development; database; the acquisition, analysis, interpretation of data; have drafted the work and substantively revised it.

CJS: Leaded the research team, research idea development, revising and approving the project design, and moderating group discussions. Also, elaborated the project's protocol and final tables and manuscripts.

ACV: The data acquisition, have drafted the work and substantively revised it. Contributed to the revision of the database, and the elaboration and revision of the tables and final manuscript.

JGPV: The data acquisition, database; have drafted the work and substantively revised it.

EVG: Acquisition and analysis of the database, and interpretation of initial data. Have drafted the work and substantively revised it

RERC: Managed the systematic search alongside MCP, created the database, collected, and interpreted data.

JASC: Acquisition and analysis of the database and interpretation of initial data. Have drafted the work and substantively revised it.

AMMR: Acquisition and analysis of the database and interpretation of initial data. Have drafted the work and substantively revised it.

AAMI: Acquisition and analysis of the database and interpretation of initial data. Have drafted the work and substantively revised it.

MAF: The design of the work, data acquisition and revision of the manuscript.
YZFS: Acquisition and analysis of the database and interpretation of initial data. Have drafted the work and substantively revised it.

JAGL: Acquisition and analysis of the database and interpretation of initial data. Have drafted the work and substantively revised it.

HLG: data acquisition, analysis, and interpretation; Have drafted the work and substantively revised it.

HBC: Acquisition and analysis of the database and interpretation of initial data. Have drafted the work and substantively revised it.

DMM: contributions to the design, data interpretation, interpretation of initial data. Have drafted the work and substantially revised it.

JP: Acquisition and analysis of the database, and interpretation of initial data. Have drafted the work and substantively revised it.

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Figures

Figure 1

PRISMA Flow Diagram

Supplementary Files

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• eAppendix.docx