Low Incidence of Symptomatic Thrombotic Events in Adult Patients Hospitalized with Coronavirus 19: A Retrospective Cohort Study

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Abstract

Background: Since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) pandemic, there have been many reports of increased incidence of venous thromboembolism and arterial events as a complication.

Objective: To determine the incidence of symptomatic thrombotic events (TEs) in patients hospitalized for SARS-CoV2 disease (coronavirus 19 [Covid-19]).

Methods: A retrospective single-center cohort study with adult patients with a positive reverse transcriptase-polymerase chain reaction (rt-PCR) for SARS-CoV2, included from the date of diagnosis of Covid-19 and followed for 90 days or until death.

Results: A total of 1621 patients were included in this study. The median age was 73 years (interquartile range25th-75th [IQR] 53-87 years) and 57% (913) were female. Overall mortality was 21.6% (348). The overall incidence of symptomatic TEs within 90 days of diagnosis was 1.8% (30 of 1621) occurring in 28 patients, including an incidence of pulmonary embolism of 0.9% (15, 95% confidence interval [CI] 0.60%-1.6%), deep venous thrombosis of 0.61% (10, 95% CI 0.2%-1%), ischemic stroke of 0.25% (4, 95% CI 0.09%-0.65%), and ischemic arterial events of 0.06% (1, 95% CI 0.008%-0.43%). No acute coronary syndrome events were recorded. The incidence of symptomatic TEs was significantly lower in the general ward than in intensive care units (1.2% vs 5.7%; p < .001). The median time since positive rt-PCR for SARS-CoV2 to symptomatic TE was 22.5 days (IQR 19-43 days). There was no significant difference in the proportion of patients receiving (53.6%) and not receiving thromboprophylaxis (66.5%) and the development of TEs.

Conclusion: The overall incidence of symptomatic TEs among these patients was lower than the incidence previously reported.

Keywords

Covid 19, thrombosis, pulmonary embolism, deep venous thrombosis

Introduction

Since the onset of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) pandemic, caused by coronavirus 19 (Covid-19), more than 225 million people have become ill worldwide, resulting in 4.6 million deaths.1 Clinical presentation range from asymptomatic patients to patients with severe pneumonia and respiratory failure requiring ventilatory support.2,3 Disease progression may lead to multiorgan failure with mortality rates from 1% to 30%, which vary by study population.4
Clinical Outcomes

The primary composite outcome was defined as the development of any of the following arterial or venous symptomatic TEs: symptomatic acute DVT of lower or upper extremities, deep visceral vein thrombosis, symptomatic acute PE, symptomatic AT, symptomatic AIS, and symptomatic ACS within a 90 days period of follow up time since enrollment. Operative definitions for the primary events were as follows: for DVT events, a positive venous echo-doppler or flebo-tomography or conventional angiography; for PE, a positive angiotomography or conventional angiography or perfusion scintigraphy or echocardiogram findings suggestive of PE combined with clinical suspicion; for AT: a positive arterial echo-doppler or conventional arterial angiography; for AIS, a compatible brain image (magnetic resonance imaging or a computed tomography scan) with a compatible clinical presentation; and for ACS, compatible symptoms with electrocardiogram and laboratory results according to treating physician notes in medical records.

As a secondary outcome, major bleeding events within the same period of time were recorded. A major bleeding event was defined according to International Society on Thrombosis and Haemostasis guidelines as fatal bleeding, symptomatic bleeding in a critical organ, or bleeding causing a fall in hemoglobin of 2 g/dl or more, or requiring transfusion of 2 or more units of whole blood or red cells. Diagnostic studies were ordered according to clinical presentation and treating physician criteria. No screening studies were ordered.

Data Acquisition, Definitions, and Confounding Analytical Variables

Data were extracted and manually validated from both the Institutional Covid-19 Registry of Hospital Italiano de Buenos Aires, as well as from each included patient EMR. Postdischarge follow-up was based on EMR revision of events of interest. Baseline demographic data, key analytical variables upon hospital admission, frequent comorbidities, and risk factors probably related to TEs such as cancer, previous TEs, surgery, pregnancy, body mass index >30, and hormonal therapy were recorded. During 90 days of follow-up time, stay length, prophylactic and therapeutic interventions, hospital readmissions, key analytical variables, and all-cause mortality were also recorded. Patients were categorized as “intensive care unit patients” (ICU patients) if at some point during hospital stay, they were admitted to a critical care area (intensive care, intermediate care, or coronary care unit), or “ward patients” for all other locations. Pharmacological TP was defined as unfractionated sodium heparin (UFH): 5000 IU bid (<100 kg), UFH 5000 IU tid (≥100 kg), or low molecular weight heparin (LMWH) as enoxaparin 40 mg qd or equivalent (<100 kg), LMWH/enoxaparin 60 mg qd or equivalent (≥100 kg), or receiving coumarin drugs or novel oral anticoagulants. Furthermore, for each patient, the number of days during hospitalization under pharmacological TP was calculated and expressed as a percentage (days under...
pharmacological TP over stay length in days). Patients were also stratified according to Padua’s prediction score for venous TEs\textsuperscript{13} in high (≥4 points) and low risk of thrombosis (<4 points).

**Statistical Analysis**

For data description, quantitative variables are presented as the mean and standard deviation or for non-normal distributed data (after histogram/normality plots and skewness/Kurtosis tests), the median and interquartile range (IQR; 25th-75th percentile). Categorical variables are reported as absolute and relative frequencies. Baseline differences between groups (with or without primary outcome) were assessed using Chi-square or Fisher’s exact test for categorical variables and the Mann–Whitney \textit{U} test or Student’s \textit{t}-test for continuous variables as appropriate. Venous/arterial symptomatic TEs incidence was calculated as the proportion of all the positive cases within the entire study population at risk during the studied period. Its corresponding 95% confidence interval (95% CI) was also calculated. The same formulation was used for estimating individual subgroups of arterial/venous TEs. To explore the association between Covid-19 and other comorbid factors, death was considered as a competitive event, and a multivariate analysis by Fine and Gray was performed, including in the model, those statistically significant variables in the initial bivariate analysis as well as those who were judged to be potential confounders such as previous prothrombotic risk factors apart from Covid-19 (cancer, previous TEs, surgery, pregnancy, increased body mass index, and hormonal therapy) and antithrombotic interventions such as different TP schedules.

**Results**

**Study Population**

From March 17 until September 30 of 2020, 1621 patients were included (Figure 1). The main reason for not fulfilling inclusion criteria was the ambulatory setting of care. All patients were followed for 90 days or until death with no patient lost to follow-up. The median age was 73 years (IQR 53-87) (Table 1). Women represented 53% (913) of the cohort, of which 6.5% (59) were pregnant. The most frequent comorbidities in the cohort are shown in Table 1. Of note, 49% (795) were obese.

Eighty-nine percent of the patients did not require admission to the ICU. For the remaining 11% admitted for critical care, 70% required invasive ventilatory support. One thousand seventy-four patients (66%) received pharmacological TP during the index admission. Basal D-dimer in patients with TEs was 3004 ng/ml (IQR 1273-4909) and 876 ng/ml (IQR 529-1655) in the non-TEs group.

Overall mortality at 90 days was 21.6% (348/1621). Mortality in the ward group was 19.5% (282/1447) while mortality in critical care units was 37.9% (66/174).

**Outcomes**

TEs were suspected in 198 patients (12.2%), who had ancillary studies depending on clinical presentation (Table 2). Thirty (12.8%) of these ancillary studies resulted in positive findings for TEs.

The cumulative incidence of the composite primary outcome was 1.8% (30 of 1621) occurring in 28 patients (Table 3). The cumulative incidence of symptomatic TEs increased in line with the patient’s severity of illness (Figure 2). The median time to develop the symptomatic TE was 22.5 days (IQR 19-43 days). The cumulative incidence of PE within the study follow-up time was 0.9% (15), while DVT cumulative incidence was 0.6% (10). There were 4 patients (0.25%) with AIS and only 1 patient with acute AT.

The majority of patients in the cohort with high-risk Padua score at admission received pharmacological TP (median distribution of the proportion of days under pharmacological TP over the length of stay in days was 83% with IQR: 64%-93%) while among those with low-risk Padua score (<4 points), pharmacological TP was lower and individualized for special situations (median of 0% with IQR: 0%-50%). In line with this standard, most of the patients with TEs were under pharmacological TP. There were no significant differences in the risk of symptomatic TEs between patients with prior use of vitamin K antagonists and patients without prior use. It is worth noting that despite most of the events occurring during index admission, 32% (9) of thrombotic complications occurred after discharge with a median time of 11 days (IQR 6-14). Mortality among those patients with at least 1 symptomatic TE was 25% (7 of 28), while for those with no event it was 21.4% (341 of 1593). Further details regarding each patient are provided in Supplemental Table 1.

Regarding secondary outcomes, four (0.25%) major bleeding events occurred in the whole cohort. Among patients without Covid-19 temporally associated TEs, two events (2 of 1593, 0.12%) were recorded: one patient had a subdural hematoma in the setting of underlying anticoagulation due to a previous event of thromboembolic disease and another one had gastrointestinal bleeding due to diverticular disease. Two major bleeding events (2 of 28, 7.1%) were registered among patients with Covid-19-related thrombosis: both patients had a hemorrhagic shock, the first event was due to a spontaneous gastroepiploic artery pseudoaneurysm bleeding in the setting of anticoagulation due to a mechanical heart valve, while the second event had retroperitoneal bleeding secondary to a lumbar artery pseudoaneurysm under treatment with acenocoumarol due to atrial fibrillation.

**Risk Factors Associated with the Primary Composite Outcome**

In a multivariate analysis to explore risk factors associated with the development of TEs, a model was built considering death as a competitive event and adjusting for age, sex, hypoxemia, and days of hospitalization. Regardless of age and sex, hypoxemia (represented as oxygen requirements or any kind of ventilatory support) and length of hospital stay (days) were independently associated with the development of events (sub hazard ratio
Discussion

This study showed a global lower incidence of TEs in admitted patients with Covid-19 than found in previous reports.\textsuperscript{5–7,14,15} A recent review by Malas et al. reports an overall incidence of venous thromboembolism of 21\% and 31\% in patients admitted to ICU.\textsuperscript{16} Incidence of any TE in the usual care arm of the biggest randomized control trial of prophylactic anticoagulation is 3.6\% in moderate patients and 11.8\% in severe patients.\textsuperscript{17} Bilaloglu et al\textsuperscript{14} found 16\% incidence of any thrombotic complication and 6.2\% of venous thrombosis with a 24.5\% all-cause in-hospital mortality. Cui et al\textsuperscript{7} report an incidence of 25\% of venous thromboembolism in a small series of 81 critical patients and Taccone et al\textsuperscript{18} report an incidence as high as 33\% in ventilated patients who underwent an angiotomography.\textsuperscript{7,18} Different from some previous cohorts that find higher TEs incidence, we only reported symptomatic events.\textsuperscript{19} This low incidence of thrombotic complications is in line with recent findings of randomized clinical trials in critical patients.\textsuperscript{20}

The lower incidence found in this cohort may be due to high adherence to antithrombotic prophylaxis with heparin, a higher denominator including noncritical patients, and a different diagnostic approach for the diagnosis of thromboembolic disease. Nevertheless, the similar positive rate results found in angiotomography studies (15\%) in this cohort, in comparison to other series, makes it less likely that this lower TE incidence would be due to a higher threshold for diagnosis.\textsuperscript{21–23} For instance, Lodigiani et al\textsuperscript{5} reported that 36\% of venous thromboembolic imaging tests were positive, with 33\% of angiotomography studies yielding positive results. Interestingly, this study by
Table 1. Population Characteristics

|                                | Total cohort (n = 1621) | Patients with thrombotic events (n = 28) | Patients without thrombotic event (n = 1593) | p  |
|--------------------------------|-------------------------|------------------------------------------|---------------------------------------------|----|
| **Age, years median (IQR)**    | 73 (53-87)              | 76 (60-88)                               | 73 (53-97)                                  | .256 |
| **Female n (%)**                | 913 (53)                | 11 (39)                                  | 902 (56)                                    | .067 |
| **Comorbidities**               |                         |                                          |                                             |     |
| Body mass index, kg/m^2 median (IQR) | 29.2 (26.1-33)          | 30.5 (27.6-33)                           | 29.2 (26.1-33)                              | .201 |
| Hypertension n (%)              | 747 (46)                | 16 (57)                                  | 731 (45)                                    | .236 |
| Diabetes n (%)                  | 189 (12)                | 1 (3.6)                                  | 188 (12)                                    | .242 |
| Chronic renal failure n (%)     | 85 (5.2)                | 3 (10.7)                                 | 82 (5.1)                                    | .178 |
| Previous thromboembolic event n (%) | 59 (3.6)              | 0                                        | 59 (3.7)                                    | NA  |
| Coronary heart disease n (%)    | 98 (6)                  | 3 (10.7)                                 | 95 (6)                                      | .237 |
| Heart failure n (%)             | 133 (8.2)               | 3 (10.7)                                 | 130 (8)                                     | .496 |
| Previous stroke n (%)           | 119 (7.3)               | 2 (7)                                    | 117 (7)                                     | NS  |
| Active cancer n (%)             | 141 (8.7)               | 3 (10.7)                                 | 138 (8.6)                                   | .730 |
| Cirrhosis n (%)                 | 6 (0.4)                 | 0                                        | 6 (0.4)                                     | NA  |
| COPD n (%)                      | 90 (5.5)                | 0                                        | 90 (5.6)                                    | NA  |
| Asthma n (%)                    | 59 (3.6)                | 0                                        | 59 (3.7)                                    | NA  |
| Tobacco use n (%)               | 252 (15.5)              | 4 (14.3)                                 | 248 (15.5)                                  | NS  |
| Pregnancy n (%)                 | 59/913 (6.5)            | 0                                        | 59/902 (6.5)                                | NA  |
| Dementia n (%)                  | 211 (13)                | 2 (7)                                    | 209 (13)                                    | .569 |
| Recent surgery n (%)            | 50 (3)                  | 2 (7)                                    | 48 (3)                                      | .213 |
| Padua score (median, IQR)       | 6 (5-7)                 | 6 (6-7)                                  | 6 (5-6)                                     | .002 |
| High risk Padua score n (%)     | 1443 (89)               | 28 (100)                                 | 1415 (88)                                   | .065 |
| **Pre-admission medicines**     |                         |                                          |                                             |     |
| Aspirin n (%)                   | 661 (41)                | 16 (57)                                  | 645 (40)                                    | .075 |
| Clopidogrel n (%)               | 28 (1.7)                | 0                                        | 28 (1.7)                                    | NA  |
| Coumarin anticoagulants n (%)   | 98 (6)                  | 3 (10.7)                                 | 95 (6)                                      | .237 |
| Hormonal therapy n (%)          | 24 (1.5)                | 0                                        | 24 (1.5)                                    | NA  |
| Antipsychotics n (%)            | 304 (18.7)              | 3 (10.7)                                 | 301 (19)                                    | .272 |
| Antidepressants n (%)           | 267 (16.5)              | 8 (28.6)                                 | 259 (16)                                    | .116 |
| Corticosteroids n (%)           | 149 (9)                 | 8 (28)                                   | 141 (8.8)                                   | .003 |
| Novel oral anticoagulants n (%) | 11 (0.7)                | 0                                        | 11 (0.7)                                    | NA  |
| **Laboratory characteristics**  |                         |                                          |                                             |     |
| Admission D-dimer ng/ml median (IQR) (n = 629) | 900 (544-1712)          | 3004 (1273-4909)                        | 876 (529-1655)                              | <.001 |
| Max D-dimer ng/ml median (IQR) (n = 629) | 1019 (571-1936)         | 3744 (1463-6264)                       | 967 (567-1846)                              | <.001 |
| Admission CRP mg/l median (IQR) (n = 680) | 48.8 (15.2-108.9)       | 88.9 (53-140.8)                         | 46.8 (14.9-108.1)                           | .048 |
| Max CRP mg/l median (IQR) (n = 680) | 55.5 (18.1-121.6)       | 88.9 (61.1-140.8)                       | 54.4 (17.4-121.3)                           | .089 |
| Admission Pro BNP pg/ml median (IQR) (n = 231) | 771.3 (256.8-3360)     | 808.5 (153.3-3534)                      | 771.3 (283.4-3360)                          | .957 |
| Max Pro BNP median (IQR) (n = 231) | 1161 (330-4476)         | 2303 (192.9-4509)                       | 1122 (338.7-4476)                           | .759 |
| **Covid-19 severity characteristics** |                         |                                          |                                             |     |
| In ward                         | 1447 (89)               | 18 (64)                                  | 1429 (89)                                   | <.001 |
| Without oxygen requirement n (%) | 1061 (73)               | 9 (50)                                   | 1052 (73)                                   | .032 |
| With oxygen requirement n (%)   | 386 (27)                | 9 (50)                                   | 377 (27)                                    | NN  |
| In ICU                          | 174 (11)                | 10 (36)                                  | 164 (11)                                    | <.01 |
| Without invasive ventilatory support n (%) | 52 (30)               | 2 (10)                                   | 50 (30)                                     | .482 |
| With invasive ventilatory support n (%) | 122 (70)               | 8 (10)                                   | 114 (70)                                    |     |
| **Hospitalization characteristics** |                         |                                          |                                             |     |
| Overall mortality within 90 days from + SARS-CoV2 rt-PCR testing n (%) | 348 (21.6)              | 7 (25)                                   | 341 (21.4)                                  | .644 |
| Length of hospital stay, days median (IQR) | 9 (4-15)                | 18 (11-30)                              | 9 (4-14)                                    | <.001 |
| Admission to ICU n (%)          | 174 (10.7)              | 10 (35)                                  | 164 (10)                                    | <.001 |
| Length of ICU stay, days median (IQR) | 10 (4-16)               | 10 (4-16)                               | 11 (7-19)                                   | .383 |
| Length of ward stay, days median (IQR) | 6 (3-10)                | 11 (6.5-14)                             | 6 (3-10)                                    | .106 |
| **Treatment during admission**  |                         |                                          |                                             |     |
| Steroids n (%)                  | 457 (28)                | 18 (64)                                  | 439 (27.5)                                   | <.001 |
| Convalescent plasma n (%)       | 45 (2.8)                | 0                                        | 45 (2.8)                                    | NA  |

(continued)
Lodigiani et al\(^5\) shows a high incidence of TEs (7.7%). Of notice, 50% of events were diagnosed within the first 24 h of admission. It can be hypothesized that those patients had a longer course of Covid-19 in an outpatient setting, without access to pharmacological TP, and therefore were only “quickly diagnosed” with established thrombotic and fibrinolytic processes, which developed prior to hospital.

In particular, the incidence of thromboembolic events in this cohort of patients with Covid-19 is similar to the incidence found in historical reports of patients without Covid-19 in the same institution (incidence of 2% during admission), and in a randomized controlled trial of critically ill patients without Covid-19 (incidence of 9.4%).\(^{24,25}\)

Even though 30% of events occurred after discharge, the absolute incidence seems too low to warrant a specific active post discharged pharmacological TP strategy. Randomized controlled trials are ongoing in this population.\(^{26}\)

Several limitations must be acknowledged. First, due to the retrospective nature of this report, missing data and misclassification of patients pose a threat to the validity of the study. Nevertheless, since no patients were lost to follow-up and data on comorbidities and clinical outcomes were collected prospectively in the Institutional Covid-19 Registry of Hospital Italiano de Buenos Aires, the effect of these factors is lessened. Second, this is the experience of a single center with patients accessing a private health care system, and therefore our study lacks a control group, so the risk of TEs in populations other than Covid-19 patients cannot be compared.

Conversely, several strengths should be remarked. First, our study reports real-world data of the overall incidence of clinically relevant TEs in a large cohort of patients with complete follow-up. Second, differently from other reports, we were able to capture both in-hospital (critical and noncritical patients) and post discharged events. Third, our study precisely collected data regarding pharmacological TP among study participants. This information may help clarify the role of prophylactic and therapeutic measures to mitigate the risk of venous and arterial TEs in patients with Covid-19. Finally, our study reports meaningful clinical outcomes of older patients than those represented in other Covid-19 registries [6, 7, 13], a population at higher risk of were less stringent, so the incidence of TEs may be underrepresented in this study, although the severity stratification used for the analysis may well correct for this phenomenon. Finally, this study lacks a control group, so the risk of TEs in populations other than Covid-19 patients cannot be compared.

Table 1. (continued)

|                  | Total cohort (n = 1621) | Patients with thrombotic events (n = 28) | Patients without thrombotic event (n = 1593) |
|------------------|-------------------------|----------------------------------------|---------------------------------------------|
| Hydroxychloroquine n (%) | 2 (0.12)                | 0                                      | 2 (0.13)                                   | NA                           |
| Lopinavir/ritonavir n (%) | 17 (1)                  | 1 (3.6)                                | 16 (1)                                     | .257                         |
| Pharmacologic thromboprophylaxis n (%) | 1074 (66)               | 15 (53.6)                              | 1059 (66.5)                                | .152                         |

Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; Covid-19, coronavirus 19 disease; CRP, C-reactive protein; BNP, brain natriuretic peptide; rt-PCR, reverse transcriptase-polymerase chain reaction; NA, not applicable; NS, nonsignificant; IQR, interquartile range; SARS-CoV2, severe acute respiratory syndrome coronavirus 2.

*High risk Padua score: a score ≥4. Nonnormal distributed variables are expressed in median and interquartile range (IQR, 25th-75th percentile)

Table 2. Cohort Thrombotic Events Diagnostic Evaluation.

| Ancillary studies during hospitalization | Total cohort (n = 1621) | Positive rate |
|-----------------------------------------|-------------------------|---------------|
| Chest angio-tomography n (%)            | 97 (6)                  | 15 (15.5)     |
| Lower extremity Doppler ultrasound n (%)| 72 (4.4)                | 8 (11)        |
| Upper extremity Doppler ultrasound n (%)| 25 (1.5)                | 2 (8)         |
| Abdominal Doppler ultrasound n (%)      | 10 (0.62)               | 1 (10)        |
| Brain magnetic resonance imaging n (%)  | 30 (1.8)                | 4 (13.3)      |
| Total of studies                        | 234                     | 12.8%         |

Abbreviations: Covid-19, coronavirus 19 disease; ICU, intensive care unit.
poor clinical outcomes and systematically underrepresented in research studies.

Conclusions
This study shows a low incidence of symptomatic TEs among hospitalized patients with Covid-19, especially in noncritical patients in comparison to previous reports. Based on these findings, we believe that the most prudent position would be not to generalize a single antithrombotic prophylactic behavior for all patients who require hospitalization due to Covid-19, but rather a more individualized strategy tailored to the local realities of each center while awaiting results of ongoing clinical trials.

Essentials

- **Background**: SARS-CoV2 infection has been associated in early studies with an increased risk of TEs.
- **Setting**: A retrospective cohort of adult patients hospitalized with Covid-19 in a tertiary teaching hospital.
- **Results**: Symptomatic TEs among these patients with Covid-19 were lower than those previously reported.
- **Significance**: factors leading to a lower incidence of symptomatic TEs among these patients should be investigated further.

Authors’ Contributions
M.G. Vallone, C. Vázquez, and F.J. Vazquez contributed to the concept, design, critical writing, and approval of the final version. F.A. Chuliber, V. Privitera, and A. Ferraris contributed to the data acquisition, concept, critical writing, and approval of the final version. R.F. Cantarella and M.F. Indo contributed to the data acquisition and approval of the final version. D.M. Sanchez Thomas and V.A. Peuchot contributed to the concept, design, and statistical analysis.

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