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Research Paper

Evaluating Post-discharge Thromboembolic Events in Patients With COVID-19

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ABSTRACT

Background: COVID-19 is associated with a high rate of thromboembolic events in hospitalized patients, but it is unclear whether this risk remains high after discharge. This study aimed to evaluate the association of underlying factors with post-discharge thrombolytic events in COVID-19 patients and the association of thrombolytic events with subsequent mortality and ischemic heart disease.

Methods: In this study, eligible patients with COVID-19 who were admitted to the respiratory ward of Loghman Hakim Hospital, Tehran, Iran, followed up for about 3 months after discharge to record any thromboembolic events. Patients who reported post-discharge thromboembolic events were confirmed based on their diagnostic tests. The Chi-square test was used to evaluate the association between thromboembolic events and qualitative parameters, and an independent t-test was used to evaluate their association with quantitative parameters. Logistic regression analysis was performed to assess the association between independent variables and the composite outcome.

Results: Thromboembolic events were diagnosed in 35 patients (5.04%), including Myocardial Infarction (MI) in 17 patients (2.44%), venous thromboembolism in 10 patients (1.44%), and ischemic stroke in 8 patients (1.15%). None of the 26 patients who received thromboprophylaxis had thromboembolic events. During follow-up, 22 patients (3.17%) died, of whom, 10 patients (43.47%) had thromboembolic events. Thromboembolic events were not associated with sedentary life and oxygen (O_2) dependency after discharge (P value of 0.40 and 0.098, respectively). Regression analyses showed that thromboembolic events were significantly associated with ischemic heart disease and mortality (P=0.007 and P<0.001, respectively).

Conclusion: Our findings support a high rate of post-hospitalization thromboembolic events in COVID-19 patients; however, it needs more large-scale trials.

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1. Introduction

Endothelial dysfunction may be induced by an infectious process and results in the thrombin generation and termination of fibrinolysis, followed by a hypercoagulable status in patients with infections [1, 2] such as COVID-19. Additionally, hypoxia in severe COVID-19 patients can trigger thrombosis via increased blood viscosity and a hypoxia-inducible factor pathway [3, 4].

The increased inflammation caused by infections leads to severe instability of hemostasis, usually seen in patients with sepsis. This severe inflammatory state has been described as an acute disseminated intravascular coagulation (DIC), characterized by decreased platelet count, prolonged prothrombin time and activated partial thromboplastin time, and increased fibrinogen degradation products such as D-dimer as well as low fibrinogen [4-6].

Since such findings were observed in sepsis in COVID-19, it shares some pathogenic mechanisms of thromboinflammation with other thrombotic microangiopathies, such as vascular damage due to inflammatory process, platelets interacting with the vascular endothelium, increased complement, and coagulation cascade activity [6].

A close relationship is observed between COVID19 and venous thromboembolism (VTE), and as our knowledge increases, this relationship will be better understood. Based on the studies reported to date, the frequency of VTE in COVID-19 patients varies. The VTE is commonly observed in intensive care patients and critically ill cases. In contrast, the literature shows heterogeneity in the use of anticoagulant prophylaxis [7-13].

Although the definite pathological effect of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection on the coagulation system is unknown, the release of various pro-inflammatory cytokines, vascular endothelial cell injuries, and platelet activation may play a role in the process. Indeed, data on coagulation activation in viral infections, such as coronaviruses, are sparse. Recently, some trail reported the emergence of antiphospholipid (APL) antibodies in 3 critically-ill COVID-19 patients with multiple cerebral infarctions [9].

Although COVID-19 is associated with a high rate of thromboembolic events in hospitalized patients, it is unclear whether this risk remains high after discharge [10].

In the present study, we aimed to evaluate the association between the underlying factors and the occurrence of post-discharge thrombolytic events in COVID-19 patients. Besides, we investigated the potential association between thrombolytic events and mortality and ischemic heart disease in these patients.

2. Materials and Methods

The study participants included 694 eligible patients with COVID-19 who were admitted to the Loghman Hakim Hospital's respiratory ward, Tehran City, Iran, from April 2020 to April 2021. We Followed patients for a minimum of 90 days and a maximum of 180 days after discharge for thromboembolic events. During hospitalization, all patients were treated according to the guidelines of Iran's Ministry of Health.

Thromboembolic events were defined as Deep Vein Thrombosis (DVT), pulmonary thromboembolism (PTE), Myocardial Infarction (MI), and ischemic stroke. DVT group included patients who had symptoms and a non-compressible venous segment in color doppler ultrasound. Patients with intraluminal filling defects in computed tomography angiography were categorized as the PTE group. Patients with new focal neurological defects for more than 24 hours, confirmed by neurologists and imaging studies, were categorized as stroke group. Finally, MI was characterized as the detection of increased and or decreased cardiac biomarker values with at least 1 value above the 99th percentile of the upper reference limit and with at least 1 of the following findings: symptoms of acute myocardial ischemia, new or presumed new significant ST-segment–T wave changes or new left bundle branch block development of pathologic Q waves in the electrocardiogram, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with ischemic etiology, or identification of an intracoronary thrombus by angiography.

Patients who had VTE during hospitalization, those who were already on long-time anticoagulation for other reasons, and patients who did not respond to our calls for follow-up were excluded from the study.

We explained our research procedure and objectives to patients or their first relatives who accompanied them in this project, and then we asked them according to our questionnaire. If we needed to visit them, it was done out of turn and free of charge. Our study was approved by the Ethics Committee of our University of Medical Sciences (IR.: SBMU.RETECH.REC.1400.545).

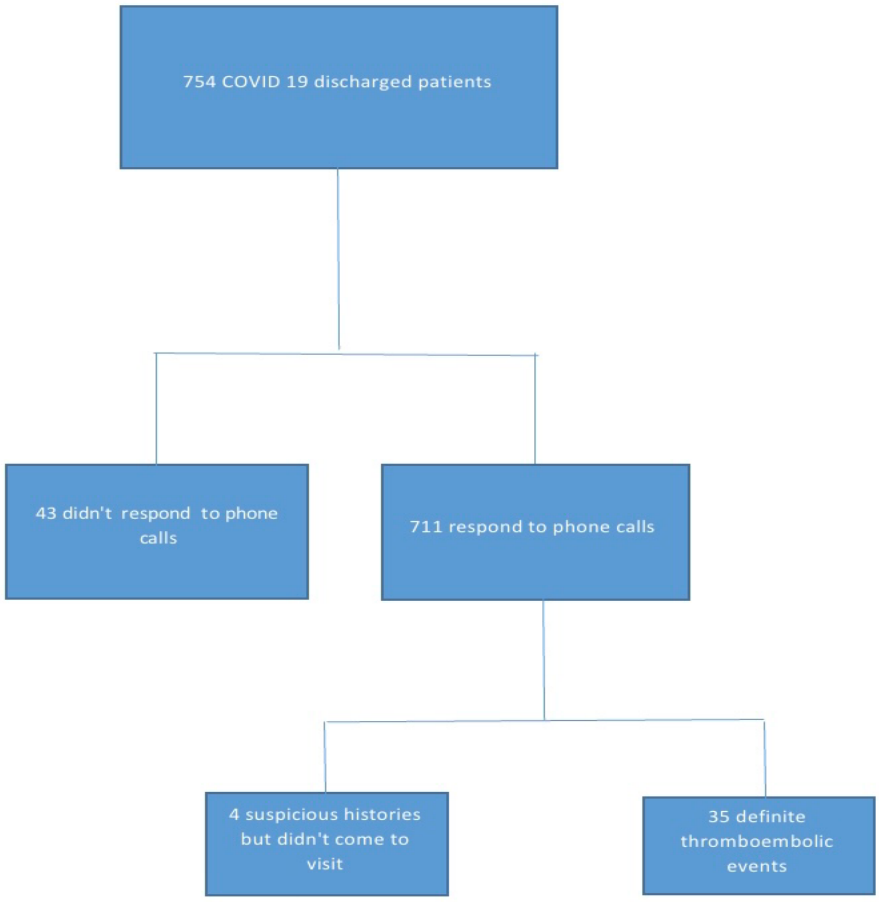

Figure 1. Flowchart of patients included in the study

We made an appointment with patients who had post-discharge thromboembolic events to confirm the diagnosis based on their diagnostic tests, although admission and released sheath of next hospital if there was evidence (Figure 1).

Our collected data included demographic characteristics, comorbidities, VTE risk factors, medications, post-discharge thromboprophylaxis, and image results were assessed for about 90 days after hospital discharge.

Data were summarized using descriptive statistics. Categorical variables were summarized using frequency and percentage; continuous variables were summarized using Mean±SD. The association between thromboembolic events and qualitative parameters was assessed by the Chi-square test. The association of these events with quantitative parameters, including age, weight, height, hospitalization period, days of Intensive Care Unit (ICU) admission, days of oxygen-dependent after hospitalization, and sedentary duration after discharge, were evaluated by the independent t-test. Logistic regression analysis was performed to assess the association between independent variables and the composite outcome. The presence or absence of thromboembolic events was considered the outcome variable for logistic regression analysis. Statistical analysis was performed using SPSS software v. 16. A 2- tailed $P<0.05$ was considered statistically significant.

3. Results

A total of 694 eligible patients with COVID-19 who were admitted to the Loghman Hakim Hospital's respiratory ward were included in this study and followed up for a minimum of 90 days and a maximum of 180 days after discharge due to thromboembolic events. According to Table 1, 368 patients (53.03%) were men, and 326 patients (46.97%) were women. The Mean±SD age of the participants was 55.1±17.7 years. Of these, 220 patients (31.7%) had hypertensive, 173 patients (24.9%) had diabetes, and 125 patients (18%) had dyslipidemia. Ninety-six patients (13.7%) were smokers. The Mean±SD hospitalization time was 6.72±1.34 days, and 25 patients (3.6%) suffered from chronic kidney disease

Table 1. Frequency of Comorbidities and Causes of Death in Study Patients

Comorbidity		No. (%)
DM		173(24.9)
HTN		220(31.7)
Hyperlipidemia		125(18)
Smoking		95(13.7)
History of IHD		89(12.8)
History of stroke		22(3.2)
CKD		25(3.6)
Cause of death	CVA	2(8.7)
	MI	8(34.8)
	Gastric cancer	1(4.3)
	Prostate cancer	1(4.3)
	Scleroderma	1(4.3)
	Unknown	10(43.5)

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DM: diabetes mellitus; HTN: hypertension; IHD: ischemic heart disease; CKD: chronic kidney disease; CVA: cerebrovascular accident; MI: myocardial infarction.

(CKD). During the follow-up, 22 patients (3.17%) died, and the cause of their death was presented in Table 1.

VTE prophylaxis with Enoxaparin (40 mg, SC) once daily was prescribed in all hospitalized patients. A total of 26 patients (3.74%) continued VTE prophylaxis after discharge for about 10 days (from 1 week to 1 month). Extended prophylaxis was done with NOAC, Warfarin, or Enoxaparin. After discharge, 29 patients (4.17%) were dependent on O2 for 14 days.

After discharge, 639 patients (92.07%) were active, and 55 patients (7.93%) had sedentary life for more than one month. After 3 months of follow-up, thromboembol-

Table 2. Comparison between basic and characteristic data and thromboembolic events

Predictor/Variables	Mean±SD		P
	Without Thromboembolic Events	With Thromboembolic Events	
Age (y)	54.6±17.6	65.5±14.7	0.001
Weight (kg)	76.3±15.1	76.4±14.5	0.967
Height (cm)	168.6±9.9	166.7±8.7	0.336
Hospitalization period (d)	7.4±5.7	6.7±5.7	0.51
ICU admission (d)	1.7±4.6	1.1±3.9	0.275
Oxygen depended after hospitalization (d)	3.35±11.8	5.07±12.8	0.098
Sedentary duration after discharge (d)	41.2±57.8	35±35	0.40

ICU: Intensive Care Unit.

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Table 3. Comparison between patients based on comorbidities and thromboembolic events

Comorbidity	Total Number n (100)	With Thromboembolic Events (n = 100)	Without Thromboembolic Events (n = 100)	P	OR (95% CI)
DM	173(24.9)	10(34.5)	163(24.5)	0.15	1.62 (0.771 to 3.432)
HTN	220(31.7)	14(48.3)	206(31.0)	0.43	2.08 (0.956 to 4.408)
Hyperlipidemia	125(18)	5(17.2)	120(18.0)	0.57	0.94 (0.385 to 2.493)
Smoking	95(13.7)	9(31)	86(12.9)	0.01	3.03 (1.292 to 6.696)
History of IHD	89(12.8)	9(31)	80(12)	0.007	3.29 (1.398 to 7.303)
History of stroke	22(3.2)	3(10.3)	19(2.9)	0.59	3.91 (1.160 to 13.49)
CKD	25(3.6)	1(3.4)	24(3.6)	0.71	0.95 (0.089 to 5.633)

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DM: diabetes mellitus; HTN: hypertension; IHD: ischemic heart disease; CKD: chronic kidney disease; OR: odds ratio; CI: confidence interval.

ic events were diagnosed in 35 patients (5.04%). These included MI in 17 patients (2,44%), VTE in 10 patients (1.44%), and ischemic stroke in 8 patients (1.15%). None of the 26 patients who received VTE prophylaxis for 10 days or longer had thromboembolic events.

Table 2 presents no significant correlation between sedentary life after discharge and thromboembolic events (P=0.40). Also, thromboembolic events were not associated with O_2 dependency (P=0.098). Instead, our analyses showed a significant association between these events and the mean age of patients, which was rational.

A significant association was observed between thromboembolic events and mortality (P<0.001). However, no significant correlation was observed between Diabetes Mellitus (DM), Hypertension (HTN), Chronic Kidney Disease (CKD), and thromboembolic events (Table 3). Also, Multivariate analysis showed a significant association between ischemic heart disease and thromboembolic events with a P=0.007 (Table 3).

4. Discussion

In our study, 5.04% of COVID-19 patients experienced post-discharge thromboembolic events, including DVT, PTE, MI, and stroke. This high incidence may be due to persistent inflammation and high-risk clinical features such as ischemic heart disease, etc. The incidence of thromboembolic events was 1.71% in the CORE-19 registry, which was less than in our study.9 In both studies, history of ischemic heart disease was a crucial predictor of thromboembolic events. During the COVID-19 pandemic, hospital visits due to other complaints such as cardiovascular problems have decreased, and people are terrified of getting infected in hospitals and clinics; therefore, people try to ignore or tolerate their symptoms. Hence, admission with COVID-19 infection had at least 2 critical effects: first, increased demand such as other diseases, and second, hypercoagulopathy states; these two may increase the risk of thromboembolic events during and after discharge.

Because of the lack of specific and guideline-based extended thromboprophylaxis after discharge in high-risk patients, and although after patients with COVID-19 patients, we do not have the same protocol for all patients and it was based on physician decision, only 26 patients (3.74%) received extended thromboprophylaxis for at least 10 days. The maximum period was 30 days.

None of our patients who received more than 10 days of VTE prophylaxis had thromboembolic events similar to the CORE-19 registry [11]. Our findings may support extended post-hospitalization thromboprophylaxis in COVID-19 patients; however, it needs more large-scale trials.

Like other studies, we found a history of ischemic heart disease and advanced age predictors of thromboembolic events. Corticosteroids such as dexamethasone were administered to all hospitalized patients for at least 5 days during admission, and we observed increased blood glucose and blood pressure during follow-up, especially in patients with preexisting disease. It may have contributed to the increased thromboembolic events in our patients, although further studies are required [12].

Among 35 patients with thromboembolic events, 22 patients (62.85%) experienced it in the first month, 8 patients (22.85) between 1-3 months, and 5 patients (14.28%) after 3 months. Therefore close follow-up of patients after discharge for at least 1 month is necessary. During the follow-up, 22 patients (3.17%) died, of whom, 10 patients (43.47%) had thromboembolic events [11].

The limitations of this study include the study sample size, lack of evaluation of other genetic and environmental factors as confounding variables, and differences between at home care of patients after discharge. In the future, we proposed to conduct a similar study with a large sample size of COVID-19 patients from multiple centers to validate the available data.

5. Conclusion

According to our study, the risk of post-discharge thromboembolic events is high in patients with COVID-19 infection, and may be extended prophylaxis is justified, especially in high-risk patients. It seems that more studies are required in this regard.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1400.545).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors decleared no conflict of interest.

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References

[1] Levi M, van der Poll T. Coagulation and sepsis. Thrombosis Research. 2017; 149:38-44. [DOI:10.1016/j.thromres.2016.11.007] [PMID]

[2] Schmitt FCF, Manolov V, Morgenstern J, Fleming T, Heimeier S, Uhle F, et al. Acute fibrinolysis shutdown occurs early in septic shock and is associated with increased morbidity and mortality: Results of an observational pilot study. Annual of Intensive Care. 2019; 9(1):19. [DOI:10.1186/s13613-019-0499-6] [PMID] [PMCID]

[3] Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. Thrombosis Research. 2019; 181:77-83 [DOI:10.1016/j.thromres.2019.07.013] [PMID]

[4] Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thrombosis and Haemostasis. 2001; 86(5):1327-30. [DOI:10.1055/s-0037-1616068] [PMID]

[5] Cattaneo M, Bertinato EM, Birocchi S, Brizio C, Malavolta D, Manzoni M, et al. Pulmonary embolism or pulmonary thrombosis in COVID-19? is the recommendation to use high-dose heparin for thromboprophylaxis justified? Thrombosis and Haemostasis. 2020; 120(8):1230-2. [DOI:10.1055/s-0040-1712097] [PMID] [PMCID]

[6] Jin S, Jin Y, Xu B, Hong J, Yang X. Prevalence and impact of coagulation dysfunction in covid-19 in China: A meta-analysis. Thrombosis and Haemostasis. 2020; 120(11):1524-35. [DOI:10.1055/s-0040-1714369] [PMID] [PMCID]

[7] Ozsu S, Gunay E, Konstantinides SV. A review of venous thromboembolism in covid-19: A clinical perspective. Clin ical Respiratory Journal. 2021; 15(5):506-12. [DOI:10.1111/crj.13330] [PMID] [PMCID]

[8] Zhang Y, Cao W, Xiao M, Li YJ, Yang Y, Zhao J, et al. [Clinical and coagulation characteristics of 7 patients with critical covid-2019 pneumonia and acro-ischemia (Chinese)]. Chinese Journal of Hematology. 2020; 41(4):302-7. [PMID] [PMCID]

[9] Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. New England Journal of Medicine. 2020; 382(17):e38. [DOI:10.1056/NEJMc2007575] [PMID] [PMCID]

[10] Rashidi F, Barco S, Kamangar F, Heresi G, A, Emadi A, Kaymaz C, et al. Incidence of symptomatic venous thromboembolism following hospitalization for coronavirus disease 2019: Prospective results from a multi-center study. Thrombosis Research. 2021; 198:135-8. [DOI:10.1016/j.thromres.2020.12.001] [PMID] [PMCID]

[11] Giannis D, Allen SL, Tsang J, Flint S, Pinhasov T, Williams S, et al. Postdischarge thromboembolic outcomes and mortality of hospitalized patients with covid-19: The core-19 registry. Blood. 2021; 137(20):2838-47. [DOI:10.1182/blood.2020010529] [PMID] [PMCID]

[12] Fontelo P, Bastola MM, Zheng Z, Baik SH. A review of thromboembolic events in hospitalized covid-19 patients. Thrombosis Journal. 2021; 19(1):47. [DOI:10.1186/s12959-021-00298-3] [PMID] [PMCID]

[13] Eswaran H, Jarmul JA, Shaheen AW, Meaux D, Long T, Saccoccio D. Vascular thromboembolic events following covid-19 hospital discharge: Incidence and risk factors. Research and Practice in Thrombosis and Haemostasis. 2021; 5(2):292-5 [DOI:10.1002/rth2.12485] [PMID] [PMCID]