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Letter to the Editors-in-Chief

Incidence of venous thromboembolic events in COVID-19 patients after hospital discharge: A systematic review and meta-analysis

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1. Introduction

During the COVID-19 pandemic, investigations have reported a high incidence of venous thromboembolic (VTE) events in hospitalized patients with coronavirus disease 2019 (COVID-19), often despite thromboprophylaxis [1,2]. However, the risk of hospital-associated VTE extends from the time of admission and over the first 90 days post hospital discharge also in COVID-19 patients. [2–6]. To this regard, the actual post-discharge cumulative incidence of VTE events in patients hospitalized for COVID-19 pneumonia has not been clearly determined, limiting the formulation of clinical recommendations regarding the need for and optimal duration of extended thromboprophylaxis strategies. The aim of this systematic review and meta-analysis is to estimate the incidence of VTE after hospital discharge among COVID-19 patients.

2. Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (Supplementary file 1). Data were obtained searching MEDLINE and Scopus for all studies published at any time up to May 15, 2021, reporting the occurrence of VTE events in COVID-19 patients after hospital discharge.

The occurrence of symptomatic or asymptomatic VTE events was chosen as the primary outcome and defined as events diagnosed within a maximum of 180 days post discharge (maximum follow-up length of revised studies) after index hospitalization. Sub-group analyses evaluating the incidence of acute pulmonary embolism (PE) and deep vein thrombosis (DVT) were also carried out as secondary outcome.

The selection of studies to be included in our analysis was independently conducted by two authors (L.R., M.Z.) in a blinded fashion. Any discrepancies in study selection were resolved by consulting a third author (G.Z.). The following MeSH terms were used for the search: “COVID-19” AND “post-discharge Venous thromboembolism” OR “Venous thromboembolism after COVID-19”. Moreover, we searched the bibliographies of target studies for additional references. Case reports, review articles, abstracts, editorials/letters, and case series with less than 10 participants were excluded. Data extraction was independently conducted by two authors (M.Z., G.R.). Studies were excluded from the meta-analysis if they did not provide data regarding the incidence of VTE events post-discharge after COVID-19 infections. For all studies reviewed we extracted the number of patients enrolled, the mean age, male gender, prevalence of potential VTE risk factors (if reported), length of follow-up, the number of VTE events as well as the number of PE and/or DVT cases when specified. The quality of included studies was graded using the Newcastle-Ottawa quality assessment scale.

The cumulative post-COVID-19 incidence of VTE events (n/N), defined as the ratio between patients experiencing VTE (n) and the number of patients enrolled in each study (N) over the follow-up period were pooled using a random effects model and presented with the corresponding 95% confidence interval (CI). Statistical heterogeneity was measured using the Higgins I^2 statistic and Q value. A predefined sensitivity analysis (leave-one-out analysis) was performed removing 1 study at the time. To evaluate the presence of publication bias both funnel plot and Egger's test were computed. Moreover, to further appraise the impact of potential baseline confounders, a meta-regression analysis using the patient's clinical characteristics, VTE risk factors, intensive care unit (ICU) admission and length of follow-up were used as moderator variables. All meta-analyses were conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, USA).

3. Results

A total of 266 articles were obtained using our search strategy. After excluding duplicates and preliminary screening, 96 full-text articles were assessed for eligibility, 87 studies were excluded for not meeting the inclusion criteria and 2 records were identified using other sources, leaving 11 investigations fulfilling the inclusion criteria (Supplementary File 2) [3–5,7–14].

Overall, 18,949 COVID-19 patients were included in this analysis (Table 1). Only four analyses reported the mean hospitalization length, which was 19.5 days [3,4,11,3]. Few investigations reported data regarding the administration of post-discharge prophylactic or therapeutic anticoagulation [3–5,10–12,14]. Eight studies also reported the rate of intensive care unit (ICU) admission during index hospitalization [4,5,8,10–14]. The mean length of follow-up was 61.7 days and follow-up duration ranged between 21 and 180 days. Quality assessment

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showed that all studies were of moderate-high quality according to the NOS scale (Supplementary file 3).

The cumulative post-discharge rate of VTE in COVID-19 patients ranged between 0.2 and 14.8% among the reviewed studies [3–5,7–14]. A random effect model revealed a pooled incidence of post COVID-19 VTE in 1.8% of cases (95% CI: 0.8–4.1%, $I^2 = 96.0\%$) (Fig. 1A). Only four studies, including 2518 patients, reported the mean time between COVID-19 discharged and VTE onset, which was 13.5 days [3,8,10,12]. Sensitivity analysis slightly changed the combined incidence rate, which remained statistically significant across a range from 1.5% of cases (95% CI: 0.5–3.0, I^2:96.0%) to 2.0% of cases (95% CI: 0.8–4.7, I^2:96.3%), suggesting that no single investigation had an undue impact on the study outcome. Both the visual inspection of the funnel plot (Supplementary file 4) and the Egger's tests revealed no evidence of publication bias ($t = 0.254$, $p = 0.804$). A further sub-analysis based only on those studies enrolling more than one-hundred patients [10–12,15,16,18,20] confirmed yielded results, showing a VTE incidence of 1.63% (95% CI:0.4–2.0%, $p < 0.0001$, I^2: 96.0%).

Not all studies differentiated between acute PE and DVT. Nine studies (n = 9199) reported the incidence of post-discharge PE after COVID-19 hospitalization, ranging between 0.2 and 5.6% [3–5,7,8–12,14]. The pooled cumulative post-discharge PE incidence was 1.5% (95% CI: 0.5–4.0, I^2:93.4%) (Fig. 1B). On the other hand, only five studies reported the incidence of post-discharge DVT after COVID-19 hospitalization, which ranged between 0.1 and 2.6% [4,8,11,12,14] (n = 7395). In these patients, the pooled cumulative post-discharge DVT incidence was 0.9% (95% CI:0.3 to 2.1, $I^2 = 78.4\%$) (Fig. 1C).

Meta-regression analysis revealed that the post-discharge incidence of VTE events was directly affected by age ($p = 0.03$) and male gender ($p = 0.04$) and inversely correlated with the length of follow-up period ($p = 0.012$). Conversely, no associations were identified using post-discharge thromboprophylaxis ($p = 0.20$), cancer ($p = 0.14$), VTE history ($p = 0.82$), ICU admission ($p = 0.55$) and mean length of hospitalization ($p = 0.68$).

4. Discussion

In this study, the pooled VTE incidence of VTE among COVID-19 patients within weeks of hospital discharge was 1.8%, which appears higher than other groups of medically ill patients [15]. Indeed, compared to the MARINER trial, the rate of 1.8% found in our study is at least 4-fold higher, which is very much in line with in-hospital data suggesting a 2-to-5-fold increased risk of VTE in the hospital phase compared to pre-COVID populations.

However, this finding resulted from very heterogeneous rates described in individual studies, which may have been due to differences in VTE screening strategies and should carefully interpreted. Indeed, it is possible that differences in follow-up strategies and presence of an immunothrombosis may have led to "overdiagnosis" of VTE in critically ill COVID-19 patients.

Most of the VTE events collected in this analysis were diagnosed early after hospital discharge, indicating that their onset depends on the changes during acute COVID-19 and on hospitalization-related risk factors. The high heterogeneity observed was partially explained by the meta-regression which supported the already previously observed relationship between VTE events and some demographical factors, such as age and male sex, as potential risk factors for VTE events in patients with COVID-19, as it is for non-COVID-19 patients [16,17]. The pathogenesis of VTE events in COVID-19 patients seems to be different and in part overlapping with "traditional" ones. Indeed, two different pathways may be identified: the former is represented by the onset of "immunothrombosis" triggered by the viral infection while the latter by the presence of "classic" major transient provoking risk factors, such as bed rest, the presence of catheters, cancer and hypoxemia, as well as age and the presence of concomitant conditions. Moreover, local endothelial cell dysfunction in the pulmonary microvasculature also seems to play a substantial role in the thromboinflammatory processes. As evidenced by our meta-regression, it seems that the second pathways predominate on the first after the resolution of the infection.

Due to the limited data provided in the reviewed manuscripts this study cannot answer the question whether extended anticoagulation may be useful for minimizing the risk of thromboembolic events after hospital discharge. In some of the reports reviewed extended thromboprophylaxis was not prescribed accordingly with current guidelines, which recommend a case-by-case evaluation, balancing the bleeding versus thrombotic risk [18]. In others, thromboprophylaxis was prescribed to a proportion of patients: therefore, our estimate may represent an underestimation of the background risk of post-discharge VTE in patients hospitalized with COVID-19. Current recommendations from the American College of Chest Physicians (ACCP) guidelines suggest that a VTE event rate $\geq$ 1% is sufficient to warrant pharmacologic

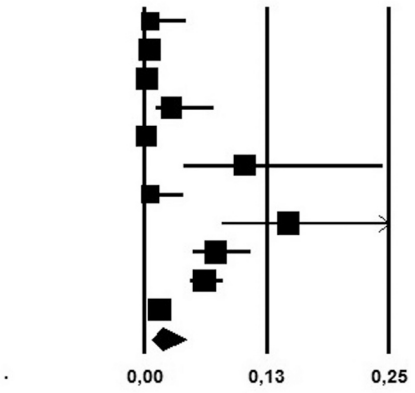
Table 1
General characteristics of the population enrolled. The summary data refer to the entire population of each study. Frequencies are reported as percentages (%). []: Interquartile range; ICU: Intensive care unit; NR: Not reported; SD: Standard deviation: VTE: Venous Thromboembolism. COPD: Chronic obstructive pulmonary disease. ° Referred to patients hospitalized in general wards; °°Referred to patients hospitalized in rehabilitation ward.*Systematic screening for VTE.

Author	Study design	Number of patients	Mean age (SD); [IQR]	Males, %	Follow-up length (days)	Thromboprophylaxis N, (%)	ICU N, (%)	COPD N (%)	Cancer N, (%)	Previous VTE
Lund et al. [15]	Population-based	8983	83 [30–56]	39.1	180	NR	NR	NR	4.4	NR
Engelen et al. [11]	Prospective*	146	58 [51–67]	62.3	42	28.0 (41/416)	39.0	NR	6.1	2.7
Rashidi et al. [12]	Observational	1529	56 [32–80]	54.4	45	4.6	7.8	9.6	NR	5.2
Roberts et al. [16]	Observational	1877	NR	NR	0	NR	11.0	NR	NR	NR
Patell et al. [10]	Retrospective	163	NR	NR	30	0	NR	NR	NR	NR
Vlachou et al. [17]	Observational	39	62.3 (15)	56.0	30	NR	NR	NR	NR	NR
Bourguignon et al. [18]	Retrospective	175	63 [48–75]°82 [75–89]°°	50.2	68.5	0	13.7	8	8.7	2.1
Parra et al. [19]	Case-Control	61	67 [59–76]	73.8	21	26.2	4.9	19.7	19.7	NR
Salisburry et al. [20]	Observational	303	73 [57–82]	54.3	90	3	22	27.3	NR	6.3
Venturelli et al. [21]	Observational	767	63 (13.6)	67.1	81	NR	8.6	4.7	3.3	NR
Giannis et al. [22]	Prospective	4906	61.7 (17.5)	53.7	92	13.2	11.8	NR	1.1	0.8

A - Venous Thromboembolism

	Statistics for each study					Weight (Random)
	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Patell	0,006	0,001	0,042	-5,072	0,000	6,71
Roberts	0,005	0,002	0,009	-15,968	0,000	9,72
Lund	0,002	0,001	0,004	-27,172	0,000	10,03
Engelen	0,027	0,010	0,071	-7,041	0,000	9,06
Rashidi	0,002	0,001	0,006	-10,783	0,000	8,75
Vlachou	0,103	0,039	0,243	-4,110	0,000	8,97
Bourguignon	0,006	0,001	0,039	-5,144	0,000	6,71
Parra	0,148	0,079	0,260	-4,858	0,000	9,63
Salisbury	0,073	0,048	0,108	-11,506	0,000	10,03
Venturelli	0,061	0,046	0,081	-18,127	0,000	10,17
Giannis	0,015	0,012	0,019	-35,914	0,000	10,22
Random effect:	0,018	0,008	0,041	-9,088	0,000	

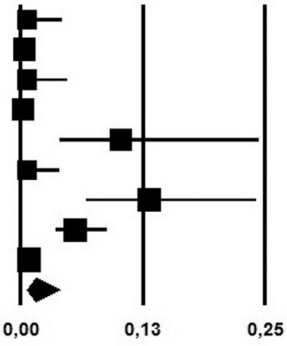
Tau-squared: 1.88; Q value: 280.0
I-squared: 96.0%, p<0.0001



B - Pulmonary Embolism

Study name	Statistics for each study					Weight (Random)
	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Patell	0,006	0,001	0,042	-5,072	0,000	8,88
Roberts	0,004	0,002	0,008	-14,756	0,000	12,31
Engelen	0,007	0,001	0,047	-4,960	0,000	8,87
Rashidi	0,002	0,001	0,006	-10,783	0,000	11,34
Vlachou	0,103	0,039	0,243	-4,110	0,000	11,61
Bourguignon	0,006	0,001	0,039	-5,144	0,000	8,88
Parra	0,131	0,067	0,241	-4,985	0,000	12,31
Salisbury	0,056	0,035	0,088	-11,307	0,000	12,78
Giannis	0,009	0,006	0,012	-30,664	0,000	13,01
Random effect:	0,015	0,005	0,040	-8,040	0,000	

Tau-squared:2.08; Q-value: 122.8
I-squared: 93.4%, p<0.0001



C - Deep vein Thrombosis

	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Roberts	0,001	0,000	0,004	-9,673	0,000	18,26
Engelen	0,007	0,001	0,047	-4,960	0,000	12,95
Parra	0,016	0,002	0,107	-4,061	0,000	12,88
Salisbury	0,026	0,013	0,052	-10,068	0,000	26,13
Giannis	0,009	0,007	0,012	-31,069	0,000	29,77
Random effect:	0,008	0,003	0,021	-10,032	0,000	

Tau-squared: 0.73; Q-value: 18.5
I-squared:78.4%, p<0.0001

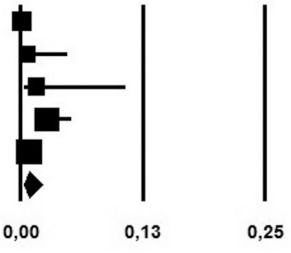


Fig. 1. Forest plots investigating the pooled incidence of post-COVID-19 venous thromboembolic events (A), acute pulmonary embolism (B) and deep vein thrombosis (C) during the follow-up period.

prophylaxis in medically ill patients: although our post-discharge VTE incidence overcomes this threshold [19], our data must be considered preliminary and cannot be directly translated into clinical practice. In a large prospective registry (CORE-19) use of post-discharge anticoagulation was associated with a 46% reduction in post discharge major thromboembolic events and mortality [14]. Prospective placebo-controlled randomized trials are needed to answer this question and are underway although one trial is poorly recruiting (i.e., ACTIVE-4c, Trial N° NCT04505774). Results from the randomized MICHELLE trial, using enrichment criteria and screening methods in hospitalized COVID-19 patients, did reveal an elevated risk of thromboembolism and a significant 67% RRR (9.43% to 3.14%, relative risk 0·33; 95% confidence interval [CI]: 0·12—0·90, p = 0.029) of major and fatal thromboembolic events favouring the direct oral anticoagulant rivaroxaban over no anticoagulation at day 35 post-hospital discharge, without increasing the bleeding events [20]. It should be noted that only one study systematically screened all patients for DVT and selected high-risk patients for PE [4] while the other reviewed reported only clinical events with patients undergoing computed tomography pulmonary angiography or lower limb ultrasound when reporting worsening of symptoms.

Our study has several limitations related to the observational nature of the studies reviewed and their own limitations with all inherited bias. Potential underestimation could derive from detection bias if patients were not systematically screened for VTE. Moreover, sampling bias by the competing risk of death may also have led to underestimation of the real cumulative incidence of thromboembolic events. We cannot assess if an adequate prophylactic anticoagulation was consistently administered as well as the outcome in patients receiving an extended thromboprophylaxis because these data were not systematically provided.

In conclusion, our study evidenced that the pooled incidence of VTE events among COVID-19 patients in the post-discharge period was elevated and estimated to be 1.8%, with acute PE representing the most frequent type of venous thromboembolic complication.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.11.029.

Declaration of competing interest

Dr. Stefano Barco reports institutional grant from Sanofi, Boston Scientific, Bayer, and Concept Medical; personal fee from Boston Scientific and Bayer outside the submitted work. Prof. Alex C Spyropoulos declare the following conflicts of interest: Research Grants and Consulting: Janssen Research & Development LLC, Bayer, Portola, Boehringer Ingelheim, Bristol-Meyers Squibb, ATLAS group outside the submitted work. Prof. Peter Verhamme reports grants and personal fees from Bayer Healthcare, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Pfizer, grants and personal fees from BMS, grants and personal fees from Daiichi-Sankyo, grants and personal fees from Leo Pharma, personal fees from Portola and Medtronic, outside the submitted work. Prof. Nils Kucher reports grants from Swiss National Science Foundation, Concept Medical, Bard, and Bayer; and personal fees from Bayer, Bard, Medtronic, Boston Scientific, BTG, and Pfizer, outside the submitted work. Prof. Stavros V Konstantinides reports grants, personal fees and nonfinancial support from Bayer AG; grants and personal fees from Boehringer Ingelheim, Actelion, Daiichy Sankyo, Biocompatibles. The other authors have no conflicts of interest to declare.

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