Significant Major Bleeding in Hospitalized Patients with COVID-19 Receiving Thromboprophylaxis

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The assessment of the thrombotic and hemorrhagic risks is essential when initiating thromboprophylaxis for the prevention of venous thromboembolism (VTE). Tan et al[1] confirmed the elevated rates of VTE in patients with coronavirus disease 2019 (COVID-19) with an overall VTE prevalence of 15%, reaching 23% in the intensive care unit (ICU). However, fewer studies evaluated the risk of major bleeding (MB). This is of importance since many institutional protocols adopted intermediate/therapeutic thromboprophylaxis dose based on the elevated risk of VTE while current guidelines recommend the use of thromboprophylaxis at a prophylactic dose in all hospitalized COVID-19 patients.[2,3] We therefore read with great interest the article of Patell et al[4] reporting a trend in higher bleeding rate in therapeutic-dose anticoagulants compared with standard-dose prophylaxis (6.3 vs. 1.7%; $p = 0.083$), advocating for further studies to define more precisely the rate of MB and guide the optimal thromboprophylaxis dosing.

As part of a systematic review on the incidence of COVID-19-related VTE (PROSPERO-CRD42020183842),[1] we also evaluated MB occurrence in hospitalized patients for COVID-19. We searched MEDLINE, Embase, and Google Scholar (January 1 to September 30, 2020). We included studies presenting the following criteria: (1) cohort of >10 patients, (2) patients with COVID-19; (3) data reporting MB. B.K.T. and J.-C.L. independently reviewed titles and abstracts of all articles, as well as full texts for deciding in their inclusion. V.M. and J.-C.L. independently extracted relevant information from selected papers. Disagreements were resolved by consensus or by consulting a third reviewer (S.P.).

The primary outcome for this subanalysis was the rate of MB in patients with COVID-19. A MB event was considered when the definition used in the study was defined according to the *International Society of Thrombosis and Haemostasis* criteria[5] or its equivalent, thereby the definition of MB could have varied across studies. The risk of bias of the selected studies, using the Methodological Index for Non-Randomized Studies (MINORS)[6] for observational studies, and the strength of the body evidence, according to the GRADE system, were evaluated independently by V.M. and S.P. Publication bias was evaluated by a funnel plot.

Overall weighted frequency of MB was analyzed using R *(meta package version 4.8–2 for pooled prevalence, R Language and Environment for Statistical Computing, Vienna, Austria)*.[7] Relative risks (RRs) were estimated with a 95% confidence interval (CI). A p-value <0.05 was considered statistically significant. $I^2 > 50\%$ was considered as substantial statistical heterogeneity. Subgroup analyses compared patients admitted to the ICU to those admitted in ICU + general ward, as well as patients receiving intermediate/therapeutic dose versus no/standard dose using Review Manager (*Version 5.3., Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014*).[8] Meta-regressions were made to evaluate association between MB and ICU hospitalization and anticoagulation intensity, respectively (rma function, metafor package).

Seventeen studies (10,722 patients) were included in our subanalysis (►**Table 1**). Seven studies[9–15] included only patients from the ICU, 6 studies[16–21] included mixed cohorts (ICU + general ward), 1 study[22] included no patients from the

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Table 1 Characteristics of studies evaluating MB in patients with COVID-19

Study	Country	Design	Patients in ICU (%)	Number of patients	Mean follow-up (days)	Male sex (%)	Age (median; interquartile range)	No A/C (%)	Prophylactic-dose A/C (%)	Intermediate prophylactic-dose A/C (%)	Therapeutic-dose A/C (%)	Major bleeding (%)
Al-Samkari et al (2020)[16]	United States	Retrospective observational study	0	256 (not critically ill)	NR	53	Mean 60 (range: 23–99)	3[a]	90[a]	NR[a,b]	NR[a,b]	1 (0)
			100	144 (critically ill)	NR	65	Mean 65 (range: 32–97)	1[a]	86[a]	NR[a,c]	NR[a,c]	8 (6)
Desborough et al (2020)[9]	United Kingdom	Retrospective observational study	100	66	28	73	59 (49–66)	0	83	0	17	7 (11)
Fraissé et al (2020)[10]	France	Retrospective observational study	100	92	NR	79	61 (55–70)	0	47	0	53	19 (21)
Hanif et al (2020)[17]	United States	Retrospective observational study	35	921	9	62	62	3	73	0	24	35 (4)
Helms et al (2020)[11]	France	Prospective observational study	100	150	7[d]	81	63 (53–71)	0[a]	70[a]	0[a]	30[a]	4 (3)
Mattioli et al (2020)[22]	Italy	Retrospective observational study	0	105	30	58	Mean: 74 ±15	0[a]	0[a]	100[a]	0[a]	2 (2)
Moll et al (2020)[18]	United States	Retrospective observational study	49	210	7	48	Mean: 62±16	9[a]	81[a]	0[a]	10[a]	2 (1)
Musoke et al (2020)[23]	United States	Retrospective observational study	NR	355	NR	51	Mean: 66±14	4	61	7	28	20 (6)
Nadkarni et al (2020)[24]	United States	Retrospective observational study	NR	4,389	NR	56	63 (53–77)	35[a]	45[a]	0[a]	20[a]	89 (2)
Paranjpe et al (2020)[25]	United States	NR	NR	2,773	5	NR	NR	2	NR	NR	28	62 (2)
Patell et al (2020)[19]	United States	Retrospective observational study	52	353 (without cancer)	8	53	61 (49–71)	7[a,e]	69[a,e]	23[a,e]	37[a,e]	32 (9)
			51	45 (active cancer)	9	49	69 (59–77)	7[a,e]	53[a,e]	13[a,e]	49[a,e]	7 (16)
Pavoni et al (2020)[12]	Italy	Retrospective observational study	100	42	30	64	Mean: 64 ±12	0[a]	0[a]	52[a]	48[a]	0 (0)
Pesavento et al (2020)[20]	Italy	Retrospective observational study	3	240 (prophylactic dose)	30	54	70 (57–81)	0[a]	100[a]	0[a]	0[a]	8 (3)
			27	84 ([sub] therapeutic dose)	30	61	77 (62–86)	0[a]	0[a]	8[a]	92[a]	8 (10)
Shah et al (2020)[13]	United Kingdom	Retrospective observational study	100	187	20	66	57 (49–64)	2[a,f]	81[a,f]	0	17[a,f]	9 (5)
Stessel et al (2020)[14]	Belgium	Retrospective observational study	100	46 (before)	30	74	70 (62–76)	0[a]	100[a]	0[a]	0[a]	0 (0)
		Retrospective observational study	100	26 (after)	30	58	62 (56–73)	0[a]	0[a]	100[a]	0[a]	1 (4)
Zermatten et al (2020)[15]	Switzerland	Retrospective observational study	100	100	NR	74	64 (56–73)	NR	NR[g]	NR[g]	8	4 (4)
Xu et al (2020)[21]	China	Retrospective observational study	15	138	NR	59	Mean: 52 ±17	NR[a]	30[a]	NR[a]	NR[a]	1 (1)

Abbreviations: A/C, anticoagulation; COVID-19, coronavirus disease 2019; DVT, deep venous thrombosis; ICU, intensive care unit; MB, major bleeding; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.

[a]At baseline.

[b]6.6% had combined intermediate and full-dose anticoagulation.

[c]2.5% had combined intermediate and full-dose anticoagulation.

[d]At least.

[e]Patients could have switched A/C group during the study.

[f]All were supposed to be on prophylactic-dose anticoagulant. Therapeutic dose was initiated if VTE was diagnosed. Three patients had no A/C and A/C was not reported for two patients.

[g]Standard-dose thromboprophylaxis until April 6, 2020, then intermediate dose.

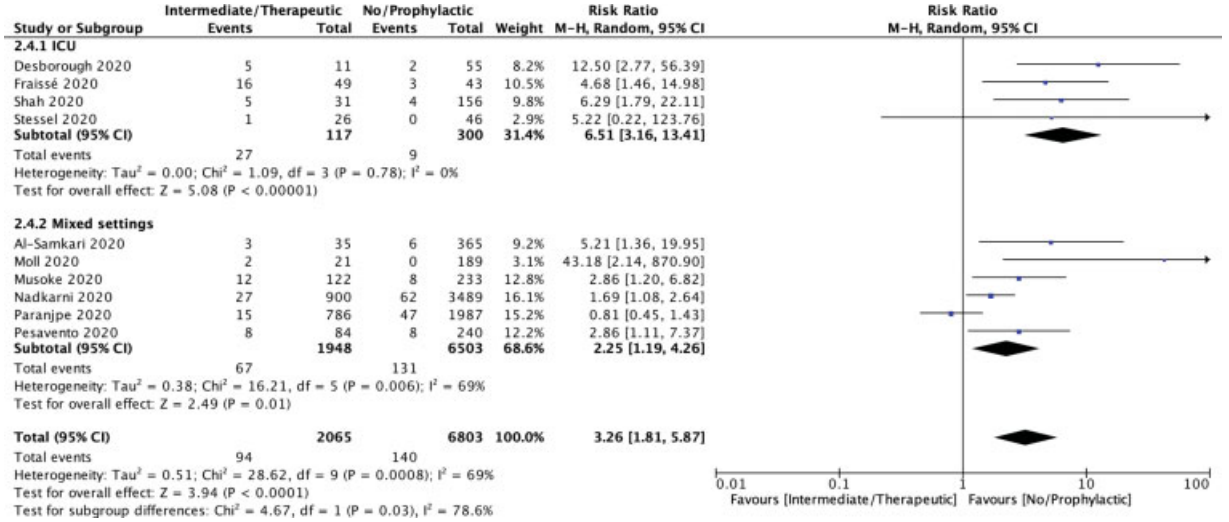

Fig. 1 Forest plot and relative risk for major bleeding (MB) in cohorts of patients hospitalized in the intensive care unit (ICU) and cohorts combining patients hospitalized in the ICU and general ward according to anticoagulation intensity. Amongst patients hospitalized in the ICU, the risk of MB was significantly increased in those receiving intermediate/therapeutic anticoagulation compared with no/standard prophylaxis at baseline. This association was also observed in cohorts combining patients hospitalized in the ICU and the general ward but to a lesser extend ($p_{interaction} = 0.03$).

ICU, and 3 studies[23–25] did not report it. At baseline, the majority of the patients were on anticoagulation at a prophylactic dose in 10 studies,[9,11,13,14,16–20,23] at an intermediate dose in 2 studies,[12,22] and at a therapeutic dose in 1 study.[10]

The overall weighted frequency of MB was 3.8% (95% CI: 2.5–5.2%; $I^2 = 89\%$; $p_{heterogeneity} < 0.01$). The funnel plot suggested publication bias. Meta-regression analyses revealed no significant association between the risk of MB and the proportion of patients hospitalized in the ICU ($p = 0.60$, 14 studies, 3,205 patients) or those receiving intermediate-/therapeutic-dose anticoagulation ($p = 0.76$, 13 studies, 3,105 patients). However, in studies including only patients hospitalized in the ICU, the risk of MB was significantly increased with intermediate/therapeutic anticoagulation versus no/standard prophylaxis (RR: 6.51; 95% CI: 3.16–13.41; $p < 0.001$) (►**Fig. 1**), occurring in 23.1% (27/117) compared with 3.0% (9/300) in patients receiving no/standard prophylaxis. This association was also observed in mixed cohorts (ICU + general ward) of patients (RR: 2.25; 95% CI: 1.19–4.26; $p = 0.01$) (►**Fig. 1**), occurring in 3.4% (67/1,948) and 2.0% (131/6,503). The median MINORS score was 9 (range: 6–12). The strength of evidence was considered very low for MB.

The present meta-analysis reports an elevated overall MB weighted frequency of 3.8%. To our knowledge, this is the largest cohort (10,722 patients) reporting the rate of MB in hospitalized patients with COVID-19. These data thus add to the article of Patell et al[4] by providing up-to-date estimates on the risk of MB. While a high proportion of patients included in this meta-analysis were treated with a prophylactic dose, the observed MB rates were markedly higher than observed in non-COVID-19 patients hospitalized for acute VTE treated with therapeutic-dose low-molecular-weight and unfractionated heparins, direct oral anticoagulants, and vitamin K antagonists, which resulted in MB in 1.5, 2.1, 1.1, and 1.7%, respectively.[26,27] The underlying mechanisms of increased MB remain elusive but may include COVID-19-related endothelialitis, platelet dysfunction, and COVID-19-associated coagulopathy.

Importantly, the incidence of MB was highly variable across studies. Consistent with previous studies, we found no association between MB and ICU hospitalization[28] or anticoagulation intensity,[4] when analyzed individually. However, subgroup analyses, considered exploratory, suggested that ICU hospitalization and anticoagulation intensity may have synergetic effects, the risk of MB being markedly elevated in critically ill patients treated with intermediate-/therapeutic-dose anticoagulation. This is further supported by a recent observational study documenting that therapeutic anticoagulation initiated within 48 hours following the admission to the ICU was associated with an increased risk of MB, occurring in 60/384 (15.6%) compared with 30/2,425 (1.2%) of patients not initially anticoagulated (RR: 5.59; 95% CI: 4.68–6.69).[29] These results may reflect the complex interplay between COVID-19 severity and anticoagulation intensity and may explain the recent pause in the recruitment of critically ill COVID-19 patients in ongoing anticoagulation trials.

We acknowledge that the present systematic review with meta-analysis presents some limitations. First, most of the studies presented data on baseline anticoagulation dosing, which may not reflect the number of patients receiving intermediate/therapeutic anticoagulation during the course of their disease. Second, confounding factors influencing bleeding (hepatic or renal insufficiency, antiplatelet therapy, and history of bleeding) could not be evaluated. Finally, our meta-regression failed to fully explain the heterogeneity associated with the risk of MB, whereas it could be partially explained by publication bias.

Our meta-analysis highlights the elevated risk of MB in hospitalized patients with COVID-19, regardless of the hospitalized setting and the anticoagulant dose. These results should be confirmed in prospective studies. Thus, the use of

thromboprophylaxis at prophylactic dose should be maintained while awaiting for results of ongoing studies.

Author Contributions

V.M. contributed to study design, completed the literature search, data collection, data analysis, data interpretation, and drafted the first version of the manuscript. S.M. contributed to data interpretation and revised the manuscript. B.K.T. completed the literature search and data collection. J.-C.L. contributed to study design, literature search, data collection, data analysis, data interpretation, and revised the manuscript. S.P. contributed to study design, literature search, data analysis, data interpretation, and wrote and revised the manuscript.

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Conflict of Interest

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