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Commentary

Venous thromboembolism and COVID-19: Mind the gap between clinical epidemiology and patient management

Michela Giustozzi *, Maria Cristina Vedovati, Giancarlo Agnelli

Internal Vascular and Emergency Medicine and Stroke Unit, University of Perugia, Perugia, Italy

Since the beginning of the coronavirus disease-2019 (COVID-19) pandemic, a compelling evidence of the association between this infection and an increased risk of venous thromboembolism has drawn the attention of scientists and clinicians, and several studies have been carried out and published on this association [1]. A meta-analysis on the incidence of pulmonary embolism (PE) in patients with COVID-19 appears in this issue of the European Journal of Internal Medicine [2]. This meta-analysis, which includes data until August 1, 2020, encompasses 22 studies for a total of 7178 patients and reports an average rate of PE of 14.7% and 23.4% in patients admitted to general wards or intensive care units, respectively.

We carried out a search on PubMed from the beginning of the pandemic until October 6, 2020 using the following terms: "COVID-19" AND "Venous thromboembolism." Overall, 317 articles were reviewed by title: 124 (39%) were narrative reviews, 51 (16%) case reports, 19 (6%) position papers or recommendations, five were editorials or letters, and six study research protocols. Among the publications, 56 were observational studies and seven were meta-analysis. The research flowchart is reported in Fig. 1.

What have we learned so far about the clinical relevance of venous thromboembolism in patients with COVID-19? In Table 1, we have summarized the main characteristics of the seven recently published meta-analyses [2–8]. The individual observational studies report the incidence and prevalence of venous thromboembolism, both PE and deep vein thrombosis (DVT), in hospitalized patients with COVID-19. About one-third of these patients have had an episode of venous thromboembolism during their disease, with a related incidence ranging from 24% to 27%. PE accounts for 16.5% of the cases (range from 11.6% to 23.4%), and DVT ranges from 7% to 14%. According to the different subgroup analyses, the incidence of venous thromboembolism increases with the severity of the disease, and therefore patients admitted to the intensive care units have the highest risk.

After reviewing the currently available literature, several clinical issues remain and the management of COVID-19 patients is still a challenge. This uncertainty may be explained by some remarkable limitations of the studies published thus far, which concern the study design, the sample size, the absence of controls, the short follow-up, and the lack of a standardized protocol on the use of thromboprophylaxis. As shown in Table 1, most of the studies were retrospective, had a relatively small simple size, and were run in a single center. In the individual studies, the administration of low-molecular-weight heparin or unfractionated heparin varied across the studies and the patients, from prophylactic to intermediate or therapeutic dose and, in some patients, different approaches were used in sequence. In most of the studies, the diagnostic workup was unclear and mainly based on a suspicion of venous thromboembolism; often times, a systematic screening for DVT

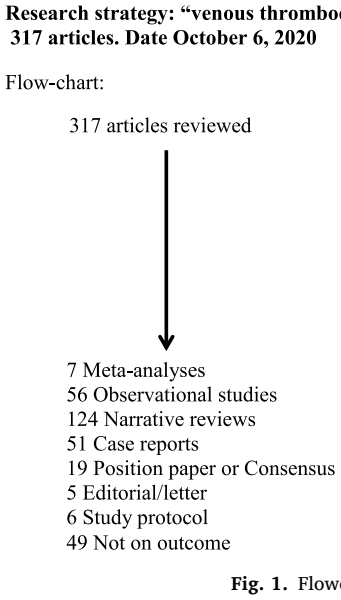

Fig. 1. Flowchart.

* Corresponding author at: Internal Vascular and Emergency Medicine and Stroke Unit, University of Perugia, Via G. Dottori, Perugia 1-06129, Italy.

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Table 1
Main characteristics of published meta-analysis.

Authors	PublicationData	No of studies	Study design	Sample size (patients)	Study outcome	Subgroup analyses	Quality assessment	Main results
Roncon et al.[2]	November 2020	23 (7178 pts)	22 retrospective 1 prospective	From 24 to 3253	Incidence of PE in pts with COVID-19	- ICU patients	NOS	*PE incidence:* 23.4% (95% CI 16.7%−31.8%, I^2 88.7%)
Di Minno et al.[3]	September 2020	20 (1988 pts)	NR	From 11 to 328	Prevalence of VTE, DVT, or PE in pts with COVID-19	- ICU patients; - Use of antithrombotic prophylaxis; - VTE screening	NR	*VTE prevalence:* 31.3% (95% CI 24.3%–39.2%); *PE prevalence:* 18.9% (95% CI 14.4%–24.3%); *DVT prevalence:* 19.8% (95% CI 10.5%–34.0%)
Porfidia et al.[4]	August 2020	30 (3487 pts)	4 prospective 22 retrospective 4 unclear	From 12 to 400	Incidence of VTE, PE and/or DVT in pts with COVID-19	- ICU patients; - Diagnostic work-up for VTE	NR	*VTE incidence:* 26% (95% PI, 6%–66%); *PE incidence:* 12% (95% PI, 2%–46%); *DVT incidence:* 14% (95% PI, 1%–75%)
Zhang et al.[5]	August 2020	17 (1913 pts)	17 retrospective	From 16 to 412	Incidence of VTE, PE and DVT in pts with COVID-19	- Severity of illness - Thromboprophylaxis rate	NOS	*VTE incidence:* 25% (95% CI, 19%–31%; I^2 95.7%); *PE incidence:* 19% (95% CI, 13%–25%; I^2 93.2%); *DVT incidence:* 7%; (95% CI, 4%–10%; I^2 88.3%)
Chi et al.[6]	August 2020	11 (1981 pts)	9 retrospective 2 prospective	From 26 to 449	Incidence of VTE, PE, and DVT in pts with COVID-19 All-cause mortality	- ICU patients - Prognostic value of the D-dimer measurement	NOS	*VTE incidence:* 23.9% (95% CI 16.2%−33.7%; I^2 93%); *PE incidence:* 11.6% (95% CI 7.5%–17.5%; I^2 92%); *DVT incidence:* 11.9% (95% CI 6.3%–21.3%; I^2 93%); *Mortality:* 21.3% (95% CI 17.0%−26.4%; I^2 53%)
Hasan et al.[7]	August 2020	12 (824 pts)	8 retrospective 2 prospective 1 cross-sectional	From 20 to 184	Prevalence of VTE, in pts with COVID-19 admitted to the ICU	- Prophylactic anticoagulation alone vs. mixed prophylactic vs. therapeutic anticoagulation	NR	*VTE prevalence:* 31% (95% CI 20%–43%)
Birkeland K et al.[8]	August 2020	14 (1677 pts)	6 retrospective 5 prospective 2 cross sectional 1 case series	From 26 to 388	Incidence of VTE in pts with COVID-19	- ICU patients - Type of thromboprophylaxis - Survivors vs. non survivors	NR	*VTE incidence:* 26.9% (95% CI 20.8–33.1)

VTE= venous thromboembolism, PE= pulmonary embolism, DVT= deep vein thrombosis, PI= prediction interval, CI= confidence interval; NR=not reported; and ICU=intensive care unit.
NOS: New Ottawa Scale.

was not performed. Furthermore, COVID-19 patients were included at different stages of their disease, which is somehow unavoidable because of the progressive nature of the patients' status.

Because of these limitations, it is not surprising that published meta-analyses reported a high heterogeneity of results making quality assessment a crucial issue. Unexpectedly, quality assessment was performed in only three out of seven meta-analyses [2,5–6]. Indeed, there are different tools to assess methodological quality in observational studies, but there is no consensus on the optimal method to assess quality. The Newcastle-Ottawa Scale (NOS), the most commonly used method to assess quality in cohort studies, was used in three of the meta-analyses [9]. The NOS scale is based on three domains: - selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study), - comparability (matched or adjusted by key factors and matched or adjusted by additional factors), - outcome (the assessment of outcome, was follow-up long enough for outcomes to occur, and the adequacy of follow-up of cohorts) [5]. The NOS scale does not have a specific cutoff score to evaluate high or low quality studies, although higher scores indicate a greater use of favorable methodological aspects. In general, the study quality is considered good when the total score is $\geq$ 5. All three meta-analyses agreed that the quality of the included studies was good or high and none of the studies had a total NOS score below 5. Why were all studies considered to be of good quality, despite the limitations mentioned above? It appears clear that during the COVID-19 pandemic, the systematic data collection or the enrolment of a significant number of patients may be a complex endeavor. In this context, the observational design allows to evaluate the real-world patient's exposure that is often a consequence of a personal choice or of life circumstances. Thus, we believe that the data on COVID-19 and venous thromboembolism have the potential to be clinically useful but their interpretation needs caution.

The main implication of the findings related to the clinical epidemiology of venous thromboembolism in patients with COVID-19 is the use of anticoagulants, mainly low-molecular-weight heparin, for the management of these patients. Valuable epidemiological data achieved by individual studies or meta-analyses of observational studies are an essential prerequisite of and provide an essential background for management studies, in particular for randomized controlled trials. Unfortunately, epidemiological data cannot replace the results of randomized controlled trials. Several position papers have been published from different scientific societies worldwide on the antithrombotic management of patients affected by COVID-19. As no randomized trial has been published so far on the management of VTE in patients with COVID-19, recommendations by a panel of experts were mainly based on observational studies and no level of evidence was reported [10–12].

Several trials comparing different dose regimens of anticoagulant interventions in hospitalized patients with COVID-19 are currently ongoing. All these trials are open-label, five of them use an adaptive design, one uses a factorial design, and two combine multiarm parallel group and factorial designs in flexible platform trials [13].

We strongly believe that at this stage there is an urgent need for well-conducted randomized controlled trials to improve the quality of evidence and thus the clinical care of patients with COVID-19, including antithrombotic prophylaxis and treatment. Based on the previous experience of clinical trials on the prevention and treatment of venous thromboembolism, we propose to start from a specific study question, to clearly define the inclusion and exclusion criteria, to establish the treatment allocation rules, to identify a control group, and plan an adequate sample size, to properly assess the study outcomes and their adjudication, and to define a specific follow-up study. It is useful to consider that the absence of adequate clinical trials might lead to an overestimation of findings from studies with modest methodology. On the other hand, this absence may preclude patients to fully benefit from therapeutic interventions of potential but improved efficacy and safety.

We appreciate that the efforts made by several investigators during the COVID-19 times were mainly driven by a generous dedication to patient care and by the desire to give a contribution to their health. However, it is no longer the time for further observational studies. We need high quality randomized controlled trials, which inevitably require a large framework of scientists and clinicians more than a proliferation of small inconclusive studies. To achieve this goal, scientists and global health professionals worldwide should collaborate to create a framework able to run clinical trials with the proper sample size and an adequate methodology.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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