Pulmonary embolism in COVID-19 infection: a high case-fatality related to pulmonary embolism characteristics

Francis Couturaud[1,2], Cécile Tromeur[1,2] and Raphael Le Mao[1,2]

[1]INSERM U1304-GETBO, Univ. Brest, FCRIN INNOVTE, Brest, France. [2]Département de Médecine Interne et Pneumologie, Centre Hospitalo-Universitaire de Brest, Brest, France.

Corresponding author: Francis Couturaud (francis.couturaud@chu-brest.fr)

Shareable abstract (@ERSpublications)
Pulmonary embolism (PE) in COVID-19 patients is associated with poorer outcomes than in non-COVID-19 patients with PE, and in COVID-19 patients without PE, emphasising the need for dedicated adequate thromboprophylactic and diagnostic strategies https://bit.ly/3QrQy7t

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The devastating outbreak of 2019 novel coronavirus disease (COVID-19) has markedly weakened healthcare systems throughout the world [1, 2]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was the first recognised main clinical presentation, which is associated with severe lung parenchymal damage, and this syndrome appeared to be the main cause of disease severity and mortality [1]. However, a few months after the pandemic started, evidence indicated that COVID-19 infection was associated with an increased risk of venous thromboembolism (VTE), and particularly pulmonary embolism (PE) and *in situ* pulmonary thrombosis [3].

Such associations are supported by a number of pathophysiological mechanisms. SARS-CoV-2 activates the coagulation pathway (including over expression of fibrinogen, thrombin, factor V and VIII) and D-dimer levels have been shown to be markedly elevated and associated with an increased mortality rate [4–6]. Immunothrombosis is also an important component, with the involvement of systemic inflammation, including neutrophils and cytokines, such as interleukin-6 [7, 8]. In addition, there is evidence that SARS-CoV-2 provokes a diffuse alveolar and endothelial damage with marked inflammation around thrombotic microangiopathy limited to pulmonary small vessels [9, 10].

In the clinical setting, the association between COVID-19 and VTE was described a few months after the start of the pandemic. Early studies, often monocentric, retrospective and of small sample size, reported a 20 to 30% frequency of PE in hospitalised patients with COVID-19, particularly in the intensive care unit setting [11, 12]. In the meta-analysis by Jimenez *et al.* [13] published in 2021, including 36 studies and more than 11 000 patients, the incidence rate of VTE in patients with COVID-19 was 17% (95% CI 13.4–20.9%) (12% for deep vein thrombosis, 7.1% for PE). However, there was a high heterogeneity in incidence estimates (incidence ranged between 5% and 85%) due to differences in study design, the administration or not of thrombo-prophylaxis and, most importantly, the setting of VTE assessment. Early in the pandemic, the Milan task force reported an incidence rate of venous and arterial thromboembolic event of 16.7% in the intensive care unit, as compared to 6.4% in general wards. Such observations have been confirmed in the meta-analysis of Jimenez *et al.* [13], where the prevalence of VTE was found to be much higher in intensive care units (27.9%) than in general wards (7.1%). Importantly, in the study of Lodigiani *et al.* [12], half of VTE was diagnosed within 24 h of hospital admission. These early key observations underlined the challenge regarding whether PE should be systematically suspected or not in a context where COVID-19 symptoms mimic PE symptoms, reinforcing the need to evaluate systematic screening of PE at hospital admission [14]. Systematic screening, as yet not recommended, may have contributed to an increase in the reported incidence of VTE, and particularly PE [14], but there was also a rapid improvement of COVID-19 management, as well as the development of dedicated vaccines. Indeed, in a more recent meta-analysis

including 66 studies with more than 23 000 patients, a lower prevalence of COVID-19-related PE was observed (7.8%, 95% CI 6.2–9.4%), which might be explained by an improvement in VTE and COVID-19 management over time and possible changes in COVID-19 severity [15].

With such limitations and rapid changes in disease management over the time, the results of large population studies provided additional important information regarding the incidence and the prognosis of COVID-19-related VTE. For example, based on the French national administrative database comparing 89 530 patients admitted with COVID-19 from 1 March to 30 April, 2020 with 45 819 patients admitted with influenza from 1 December, 2018 to 28 February, 2019, the incidence rates of VTE and PE in patients with COVID-19 were 4.9% and 3.4%, respectively, and 1.7% and 0.9%, respectively, for patients with influenza [16]. Similarly, in the Spanish population-based study of 74 814 patients with COVID-19 admitted to emergency wards, the standardised incidence of PE in COVID-19 patients was 310 per 100 000 person-years compared to an incidence of 35 per 100 000 person-years (OR 8.95, 95% CI 8.51–9.41) in patients without COVID-19 [17]. Thus, the increased incidence of VTE in COVID-19 was consistently observed in numerous clinical studies and population-based studies.

Such large studies also underlined that the presence of VTE in hospitalised patients with COVID-19 could be associated with a greater disease severity and an increased mortality [18, 19]. Indeed, it has been shown that COVID-19 patients with PE more often require mechanical ventilation and admission to the intensive care unit [18, 19]. However, it is still uncertain whether the reported mortality in PE patients with COVID-19 is directly related to PE or not. In the Spanish registry, the in-hospital mortality in COVID-19 patients with PE (16.0%) was: 1) similar to that in COVID-19 patients without PE (16.6%; OR 0.96, 95% CI 0.65–1.42); and 2), higher than in non-COVID-19 patients with PE (6.5%; OR 2.74, 95% CI 1.66–4.51) [17]. Conversely, in the large UK multi-sourced nationwide cohort study of 272 423 patients admitted to 195 hospitals with thromboembolic events between February 2018 and July 2020, the incidence of thromboembolism increased by 45.9% and the mortality from thromboembolism increased by 6.7% during the COVID-19 pandemic, as compared to the historical baseline, with more thromboembolism deaths occurring in the community compared with the historical rate (44% *versus* 33%) [20].

Facing this uncertainty, the study of Hobohm *et al*. [21] presented in this issue of the *European Respiratory Journal* provides important additional information. The authors analysed the German nationwide inpatient database that included 176 137 patients hospitalised in 2020 for COVID-19 infection. The objectives were to compare: 1) incidence and mortality rates between COVID-19 patients with and without PE during the year 2020; and 2) PE prevalence and case fatality rates between PE patients with COVID-19 (year 2020) and PE patients without COVID-19 (year 2019). The most striking results of are related to the severity and the mortality of PE associated with COVID-19 during the year 2020: 1) the case fatality in patients with COVID-19 and PE was found to be much higher (28.7%) as compared to that in COVID-19 patients without PE (17.7%); 2) COVID-19 patients with PE more often developed acute respiratory distress syndrome as compared to COVID-19 without PE, and were more often treated in the intensive care unit with a higher rate of mechanical ventilation, dialysis and extracorporeal membrane oxygenation; 3) PE patients with COVID-19 infection had more often severity criteria, including right ventricular dysfunction, shock, cardiopulmonary resuscitation and a higher case-fatality (28.7% *versus* 13.1%) as compared to PE without COVID-19; and 4) COVID-19 infection was associated with a 3.1-fold increased risk of case fatality in patients with PE as compared to patients with PE and without COVID-19. When comparing 2019 and 2020, the case fatality rate was slightly higher in 2020 as compared to 2019, although the number of hospitalisations for PE was similar. Of note, in such large database, diagnostic screening and assessment has not been adjudicated and a lower prevalence of PE (1.9%) than that observed previously was reported. Nevertheless, previously recognised risk factors for PE in COVID-19 patients were found, such as male sex, obesity and cancer, these findings reinforcing the validity of the analyses.

These findings, based on one of the largest study populations, confirms the poorer prognosis of PE in COVID-19 patients as compared to PE in non-COVID-19 patients and COVID-19 patients without PE, which is complementary to other studies [20]. These results are important for clinical practice as they highlight the need for adequate thromboprophylaxis but also adequate screening for PE in COVID-19 patients. To date, such dedicated recommendations on the optimal diagnostic strategy for PE are lacking and the optimal thromboprophylaxis in terms of dose and duration is still uncertain.

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content: all authors. Final approval of the manuscript: all authors. Administrative, technical or material support: all authors.

Conflict of interest: F. Couturaud reports having received research grant support from Bayer and Bristol-Myers Squibb/Pfizer, and fees for board memberships or symposia from Bayer, Bristol-Myers Squibb/Pfizer, Sanofi, Leopharma and AstraZeneca, and having received travel support from Bayer, Bristol-Myers Squibb/Pfizer and Leo Pharma. C. Tromeur declares she has no conflict of interest related to this research. R. Le Mao declares he has no conflict of interest related to this research.

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