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Incidence and mortality of pulmonary embolism in COVID-19: a systematic review and meta-analysis

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Coronavirus disease 2019 (COVID-19) remains an increasing global pandemic, with significant morbidity and mortality. Severe complications of COVID-19 associated with coagulation changes, mainly characterized by increased D-dimer and fibrinogen levels with higher thrombosis risk, in particular pulmonary embolism (PE), have been reported recently [1]. However, the epidemiology of PE among COVID-19 patients is currently only based on small case series and retrospective studies. This systematic review and meta-analysis addresses this gap in knowledge, facilitating first-line healthcare providers' understanding of PE incidence and mortality in COVID-19.

Relevant Chinese or English language studies were identified by systematic search of EMBASE and PUBMED from inception to June 28, 2020, using the keywords "COVID-19," "pulmonary embolism," "incidence," "prevalence," and "mortality" with appropriate MeSH terms, whereby the reference lists of identified studies yielded additional sources. We excluded conference abstracts, other types of publications (e.g., editorials, review articles, commentaries and treatment consensus), and studies lacking PE incidence or mortality rate reports. Two reviewers (SCL, SCS) screened the titles and abstracts for relevance, independently assessed the full texts of the screened search results, and drew up a final list of studies for inclusion through discussion and only after reaching full agreement. All statistical analyses were performed using MedCalc (Windows) version 15.0 (MedCalc Software, Ostend, Belgium). Incidence and mortality rates of PE in COVID-19 are represented as proportions with 95% confidence interval (CI), using the random effects model, and displayed as Forest plot. Heterogeneity among the studies was detected by Cochran Q test, whereby a p value < 0.10 indicated significant heterogeneity. We assessed the proportion of variation in study estimates attributable to heterogeneity through the I^2 statistic.

We excluded 78 out of 97 articles screened: 20 studies were duplicates, 5 were irrelevant, 3 were conference abstracts, 21 were other types of publications, 28 lacked data on PE incidence or mortality, and 1 was published in French. Ultimately, our analysis included 19 articles, mostly from Europe (84%), and we summarize their demographic data in Table 1. Overall, the incidence and mortality rate of COVID-19 patients developing PE was 15.3% (95%: 9.8–21.9) and 45.1% (95%: 22.0–69.4), respectively. Some evidence of statistical heterogeneity among the studies reporting PE incidence (I^2: 92.0%, $p < 0.001$) and mortality (I^2: 78.6%, $p < 0.001$) in COVID-19 was observed (Fig. 1).

With increasing reports of PE following COVID-19 infection, our findings indicate that nearly 2 in 10 developed PE among a total of 1835 COVID-19 patients. Immobilization, inflammation, activated coagulation, and suppressed fibrinolysis have been proposed to explain the occurrence of PE in COVID-19 patients; however, the incidence of PE in COVID-19 patients is higher than in

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Table 1 Study characteristics

First author (Year)	Study design	City (country)	Male (%)	Age (median, years)	Settings	PE diagnosis	D-dimer (median, mg/dL)	Prophylactic anticoagulation (%)	Mechanical ventilation (%)	ARDS (%)	Overall mortality (%)
Asia											
Wang Y (2020) [2]	RCT (remdesivir group)	Beijing (China)	56	66	Inpatient	NA	NA	NA	7	10	15
Wang Y (2020) [2]	RCT (placebo group)	Beijing (China)	65	64	Inpatient	NA	NA	NA	13	8	13
America											
Riker RR (2020) [3]	Case series	Portland (USA)	NA	NA	Inpatient (ICU)	CTPA	NA	NA	100	100	NA
LeBrun DG (2020) [4]	Retrospective cohort	New York (USA)	33	87*	Inpatient (ICU, ward)	NA	NA	NA	33	NA	56
Europe											
Wichmann D (2020) [5]	Case series	Hamburg (Germany)	75	73	Mortuary	Autopsy	90.4	33	33	NA	100
Klok FA (2020) [6]	Retrospective cohort	Leiden (Netherlands)	76	64*	Inpatient (ICU)	CTPA	NA	100	NA	NA	22
Llitjos JF (2020) [7]	Retrospective cohort	Pairs (France)	77	68	Inpatient (ICU)	CDU	1.8	31	100	81	12
Helms J (2020) [8]	Prospective cohort	Strasbourg (France)	81	63	Inpatient (ICU)	CTPA	2.3	100	100	100	9
Menter T (2020) [9]	Retrospective cohort	Basel (Switzerland)	81	76*	Mortuary	Autopsy	4.0	NA	30	NA	100
Florian Bompard (2020) [10]	Retrospective cohort	Paris (France)	70	64	Inpatient, outpatient	CTPA	1.6	53	13	NA	12
Hékimian G (2020) [11]	Retrospective cohort	Paris (France)	NA	NA	Inpatient (ICU)	CTPA or autopsy	NA	NA	NA	NA	NA
Artifoni M (2020) [12]	Retrospective cohort	Nantes (France)	61	64	Inpatient (ICU, ward)	CTPA	0.8	99	11	NA	NA
Fraissé M (2020) [13]	Retrospective cohort	Argenteuil (France)	79	61	Inpatient (ICU)	CDU	2.4	47	89	NA	41
Thomas W (2020) [14]	Retrospective cohort	Cambridge (UK)	69	20–29: 2% 30–39: 5% 40–49: 13% 50–59: 29% 60–69: 22% 70–79: 27% 80–89: 3%	Inpatient (ICU)	CTPA	0.4	NA	83	NA	16
Lodigiani C (2020) [15]	Retrospective cohort	Milano (Italy)	68	66	Inpatient (ICU, ward)	CTPA	Survivors: Day 1–3: 0.4 Day 4–6: 0.4 Day 7–9: 0.5	79	NA	NA	26

Table 1 Study characteristics *(Continued)*

First author (Year)	Study design	City (country)	Male (%)	Age (median, years)	Settings	PE diagnosis	D-dimer (median, mg/dL)	Prophylactic anticoagulation (%)	Mechanical ventilation (%)	ARDS (%)	Overall mortality (%)
							Non-survivors: Day 1–3: 0.9 Day 4–6: 0.9 Day 7–9: 1.5				
Poissy J (2020) [16]	Case series	Lille (France)	NA	NA	Inpatient (ICU)	CTPA	NA	NA	63	63	14
Gervaise A (2020) [17]	Retrospective cohort	Saint Mande Cedex (France)	75	62*	Outpatient	CTPA	3.6*	NA	57	NA	15
Longchamp A (2020) [18]	Case series	Sion (Switzerland)	64	68*	Inpatient	CTPA	2.1	96	92	NA	20
Leonard-Lorant I (2020) [19]	Retrospective cohort	Strasbourg (France)	66	64	Inpatient (ICU, ward)	CTPA	PE: 15.4 Non-PE: 1.9	46	NA	NA	NA
Grillet F (2020) [20]	Retrospective cohort	Besancon (France)	70	66*	Inpatient (ICU, ward)	CTPA	NA	NA	34	NA	NA

*In studies not reporting the median, results are represented by the mean

CDU complete duplex ultrasound, *CTPA* CT pulmonary angiography, *ICU* intensive care unit, *NA* not available, *PE* pulmonary embolism, *RCT* randomized controlled trial

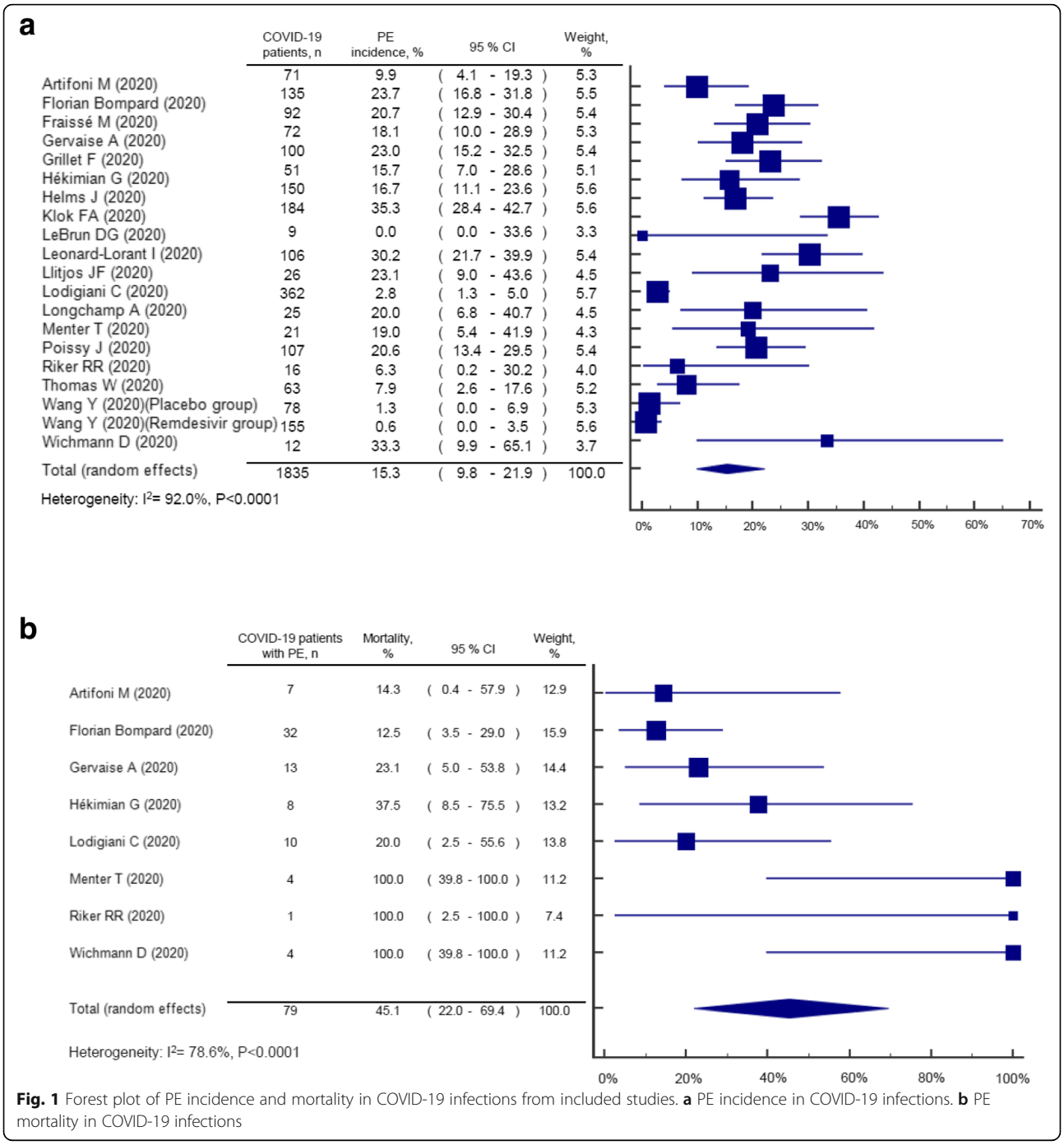

Fig. 1 Forest plot of PE incidence and mortality in COVID-19 infections from included studies. **a** PE incidence in COVID-19 infections. **b** PE mortality in COVID-19 infections

patients with seasonal and pandemic influenza (3%) [21]. In addition, our report indicates COVID-19 patients with PE may have up to 45% higher mortality rate compared to general cases (in-hospital mortality rate 4%) [22]. Therefore, first-line healthcare providers should be vigilant about the occurrence of severe and potentially fatal PE complications in COVID-19 patients [23].

As far as we know, this systematic review is the first summarizing PE incidence and mortality in COVID-19 patients. However, caution is advised in interpreting our findings. First, most published literatures are observational studies, making it difficult to confirm causality between COVID-19 and PE. Second, clinical heterogeneity between studies is noteworthy; for example, the included studies apply different diagnostic tools of varying sensitivity and specificity to investigate PE incidence. In conclusion, prevention and control of COVID-19 remains paramount in the current

pandemic, but repeated assessment and optimal management of PE complications may significantly modify the prognosis and reduce mortality in patients with COVID-19 [24].

Abbreviations
PE: Pulmonary embolism; CI: Confidence interval; COVID-19: Coronavirus disease 2019

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SCL and SCS contributed equally to this work. SCL and SCS: critical analysis, interpretation of the data, and drafting of the manuscript. MJH and YCC: study supervision and administrative, technical, or material support. All authors read and approved the final manuscript.

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