Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Internal Medicine 82 (2020) 29–37

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Incidence of acute pulmonary embolism in COVID-19 patients: Systematic review and meta-analysis.

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ARTICLE INFO

Keywords:
Pulmonary embolism
Covid-19
Epidemiology
Meta-analysis

ABSTRACT

Background: Acute pulmonary embolism (PE) has been described as a frequent and prognostically relevant complication of COVID-19 infection.
Aim: We performed a systematic review and meta-analysis of the in-hospital incidence of acute PE among COVID-19 patients based on studies published within four months of COVID-19 outbreak.
Material and Methods: Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in abstracting data and assessing validity. We searched Medline, Scopus and Web of Science to locate all articles published up to August 1, 2020 reporting the incidence of acute PE (or lung thrombosis) in COVID-19 patients. The pooled in-hospital incidence of acute PE among COVID-19 patients was calculated using a random effects model and presenting the related 95% confidence interval (CI). Statistical heterogeneity was measured using the Higgins I^2 statistic.
Results: We analysed data from 7178 COVID-19 patients [mean age 60.4 years] included in twenty-three studies. Among patients hospitalized in general wards and intensive care unit (ICU), the pooled in-hospital incidence of PE (or lung thrombosis) was 14.7% of cases (95% CI: 9.9–21.3%, $I^2 = 95.0\%$, $p < 0.0001$) and 23.4% (95% CI:16.7–31.8%, I2 = 88.7%, $p < 0.0001$), respectively. Segmental/sub-segmental pulmonary arteries were more frequently involved compared to main/lobar arteries (6.8% vs18.8%, $p < 0.001$). Computer tomography pulmonary angiogram (CTPA) was used only in 35.3% of patients with COVID-19 infection across six studies.
Conclusions: The in-hospital incidence of acute PE among COVID-19 patients is higher in ICU patients compared to those hospitalized in general wards. CTPA was rarely used suggesting a potential underestimation of PE cases.

1. Introduction

The outbreak of coronavirus disease 2019 (COVID-19) remains a severe public health emergency of international concern. Over the past months, several investigations have suggested an association between the COVID-19 pathogenesis and a pro-coagulant pattern that seems to be implicated in a higher risk of both arterial and venous thrombotic events [1-7]. In this regard, acute pulmonary embolism (PE) has emerged as a potential severe complication of the infection and both American and European consensus statement have suggested general recommendations to deal with these clinical events [8-11]. However, the actual in-hospital incidence of acute PE in these patients has not yet been determined, but autopsy studies suggested that PE or lung thrombosis may represent a frequent cause of death in COVID-19 patients (Ref Ann Int Med). Indeed, radiological assessment with CT pulmonary angiography (CTPA) was not always feasible, especially in patients hospitalized in intensive care units (ICUs) during the first months of the pandemics, also due to critical illness and the frequent need of pronation during mechanical ventilation [12]. A more reliable estimation of the extent of this complication appears essential to guide the management of these patients. The aim of the present study is to perform a systematic review and meta-analysis on the in-hospital incidence of acute PE in COVID-19 patients hospitalized in general wards and ICUs based on studies published so far.

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https://doi.org/10.1016/j.ejim.2020.09.006
Received 16 May 2020; Received in revised form 2 September 2020; Accepted 6 September 2020
Available online 17 September 2020

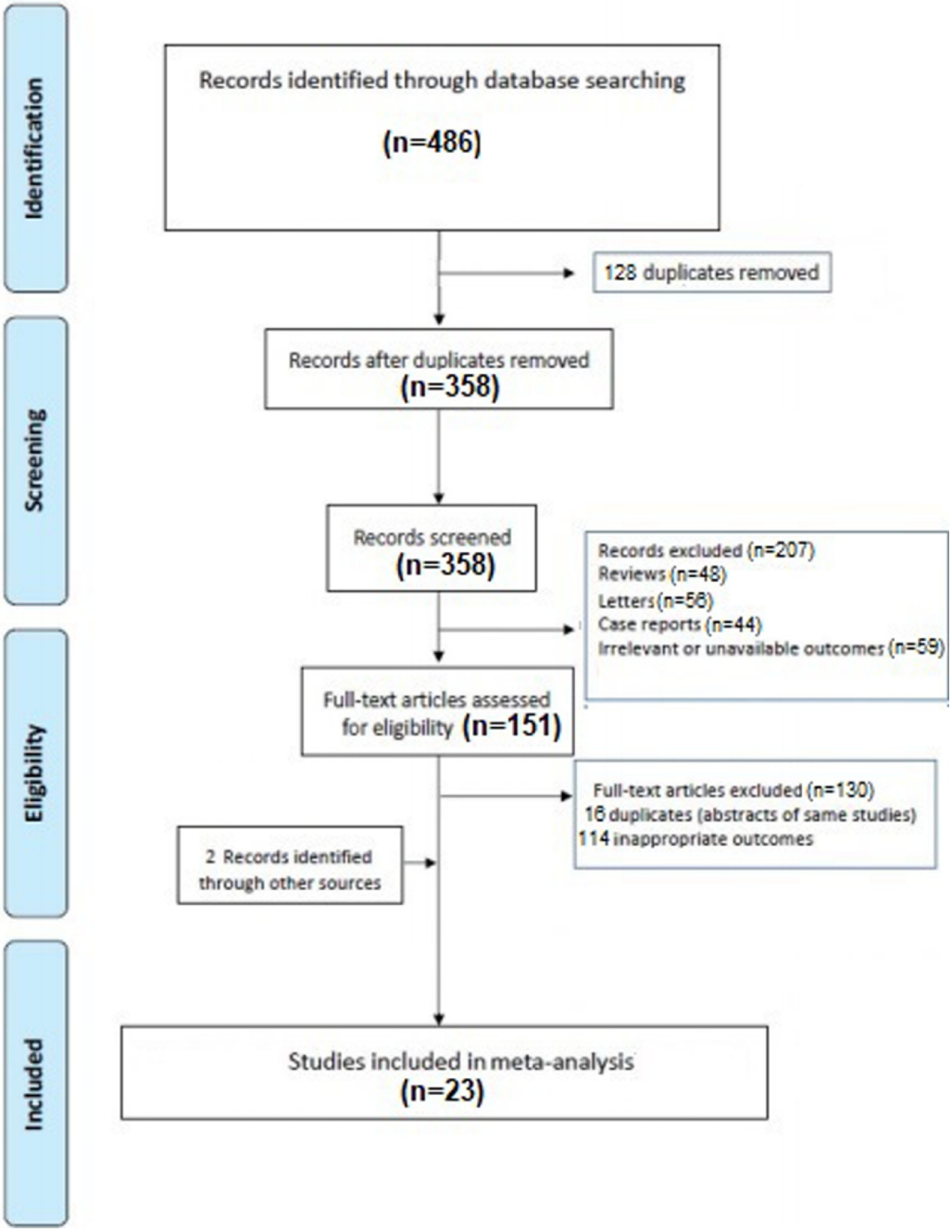

Fig. 1. Flow diagram of selected studies for the meta-analysis according to the Preferred reporting items for systematic reviews and meta-analyses (PRISMA).

2. Material and methods

2.1. Study design and eligibility criteria

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (Supplementary file 1) [13]. Data were obtained searching MEDLINE, Scopus and Web of Science for all investigations published any time to August 1, 2020 reporting the occurrence of acute PE in COVID-19 patients during the hospitalization.

2.2. Outcomes

The in-hospital incidence of acute PE in COVID-19 patients hospitalized into intensive care unit (ICU) and general wards was chosen as the primary outcome. Conversely, the anatomic location of thromboembolism within the pulmonary arterial vasculature and the use of CTPA for the diagnosis of acute PE were selected as the secondary outcomes.

2.3. Data extraction and quality assessment

The selection of studies to be included in our analysis was independently conducted by 2 authors (L.R., M.Z.) in a blinded fashion. Any discrepancies in study selection was resolved by consulting a third author (P.Z.). The following MeSH terms were used for the search: “COVID-19″ AND (“Pulmonary embolism” OR “Thrombosis” OR “Venous thromboembolism”). 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 2 authors (M.Z., P.Z). Studies were excluded from the meta-analysis if they did not provide data regarding the incidence of acute PE among COVID-19 patients. For all studies reviewed we extracted the number of patients enrolled, the mean age, male gender, prevalence of common cardiovascular comorbidities (if reported), the number of acute PE observed in patients hospitalized in ICU or general wards, the use of CTPA and the anatomic location of pulmonary emboli. The quality of included studies was graded using the Newcastle-Ottawa quality assessment scale [14].

2.4. Data synthesis and analysis

Continuous variables were expressed as mean ± standard deviation (SD) or as median with corresponding interquartile range, categorical variables as counts and percentages. The cumulative in-hospital incidence of acute PE (n/N), defined as the ratio between patients experiencing acute PE (n) and the number of patients enrolled in each study (N), hospitalized in general wards and ICUs 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. A $I^2 = 0$ was considered to indicate no heterogeneity, values of I^2 as $<25\%$, 25–75% and above 75% to indicate low, moderate, and high degrees of heterogeneity, respectively [15]. To evaluate publication bias both Egger's test and funnel plots were computed. Data regarding the anatomical distribution of intraluminal pulmonary artery filling defects and the use of CTPA were calculated by extracting numerators and denominators separately and independently from the individual studies. The difference between the main/lobar versus segmental/subsegmental pulmonary arteries was compared using the Pearson's $\chi 2$ test. All meta-analyses were conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, USA).

3. Results

3.1. Search results and included studies

A total of 486 articles were obtained with our search strategy. After excluding duplicates and preliminary screening, 151 full-text articles were assessed for eligibility and 130 studies were excluded for not meeting the inclusion criteria, leaving 23 investigation fulfilling the inclusion criteria (Fig. 1) [1,3,4,8,12,16-33].

3.2. Characteristics of the population and quality assessment

Overall, 7178 COVID-19 patients [mean age 60.4 years] were included in the analysis. The general characteristics of the studies included are showed in Table 1. Although the concomitant comorbidities were not systematically recorded by all investigations, active cancer and previous venous thromboembolic events were reported in a small percentage of cases. Fourteen studies considered ICU patients [1,3,4,8,16-20,22,25,26,28] while fifteen provided data of subjects hospitalized in general wards [1,8,17,20,21,23,24,26-33]. Seven studies reported the data of both ICU and general wards patients [1,8,17,19,20,26,28]. Quality assessment showed that all studies were of moderate-high quality according to the NOS scale (Supplementary file 2) [14].

3.3. Pooled in-hospital incidence of acute pulmonary embolism in icu and general wards

The cumulative in-hospital rate of acute PE in COVID-19 patients hospitalized in general wards ranged between 1.6 to 62.5% among six studies [1,8,17,20,21,23,24,26-33]. A random effect model revealed a pooled incidence of acute PE in 14.7% of cases (95% CI: 9.9–21.3%, $I^2 = 95.0\%$) (Fig. 2, panel A). Higher rates were reported in ICU patients, ranging between 4.2 to 75.0% in the ten studies reviewed [1,3,4,8,16-20,22,25,26,28]. In these patients, a pooled cumulative incidence rate of acute PE was 23.4% (95% CI:16.7–31.8%, $I^2 = 88.7\%$) (Fig. 2, panel B).

3.4. Assessment of publication bias

The Egger's tests revealed no evidences of publication bias in estimating the pooled incidence of acute PE among patients admitted in general wards or ICU ($t = 0.065$, $p = 0.978$ and $t = 0.591$, $p = 0.565$, respectively). A visual assessment of the funnel plot cannot reassure about the presence of an asymmetry with studies characterized by higher PE rate being missing at the basis of the triangle (Supplementary file 3).

3.5. Imaging techniques adopted and deep vein thrombosis

Most of the studies reviewed used CTPA for the diagnosis of PE. Only one study reported the use of transthoracic echocardiography in two patients for the diagnosis [3]. Prophylactic and therapeutic anticoagulation resulted largely used in the studies reviewed using different drugs such as enoxaparin, dalteparin and unfractionated heparin (UFH) as well as different regimens. However, very few investigations reported the number of PE patients treated before the diagnosis of acute PE, as shown in Table 2. The analysis of the prevalence of concomitant DVT [1,21–28,30,33] ranged between 1.5% [8] to 33.3% [27].

3.6. Anatomical location of acute pulmonary embolism and use of ctpa

The studies reviewed did not systematically report the anatomical location of the pulmonary emboli in the arterial tree or classified the anatomical location heterogeneously. In fifteen studies that reported the former information, arterial filling defects at CTPA, calculated by extracting numerators and denominators separately and independently from the individual studies, involved the main, lobar, segmental and subsegmental pulmonary arteries in 8.3% ($n = 85/1023$), 7.8%, ($n = 102/1299$), 12.2% ($n = 189/1544$) and 11.4 ($n = 107/1025$) of cases, respectively [1,4,8,16–21,24,25,27,30,31]. Segmental/sub-segmental were more frequently involved compared to main/lobar arteries (6.8% vs18.8%, $p < 0.001$) (Fig. 3). Moreover, in the thirteen studies that reported how many patients underwent CTPA, it was used only in 35.3% ($n = 1957/5532$) of patients with COVID-19 infection (Table 2) [1,8,12,16,17,19,24–26,28,31–33].

4. Discussion

We performed a pooled analysis of the rate of acute PE in COVID-19 patients including data collected during the first months after the COVID-19 outbreak. The in-hospital rate of acute PE was higher in ICU patients than in those hospitalized in general wards. The most common sites in which pulmonary filling defect were observed using CTPA appeared to be the lobar and segmental pulmonary arteries. However, CTPA was only used in a selected group of patients, approximately one-third of total, indicating that underdiagnosis was likely and, consequently, missed PE events may have contributed to the high mortality recorded among COVID-19 hospitalized patients. This uncertainty is reflected by the extreme clinical and statistical heterogeneity of these results.

Previous analyses have estimated a significant lower incidence of acute PE in the ICU population, which generally increase in mechanically ventilated patients [34,35]. The high incidence of acute PE in critically ill patients may reflect a more severe pro-coagulant state [36–39]. Indeed, as shown by the general characteristics of the patients reviewed, both active cancer and previous venous thromboembolic events were uncommon and unlikely to explain the burden of thromboembolic complications beyond a contributing role.

Table 1
General characteristics of the population enrolled. The summary datarefer to the entire population of each study. Frequencies are reported as count (%). []: Interquartile range; ICU: Intensive care unit; NOS: Newcastle-Ottawa quality assessment scale; NR: Not reported; SD: Standard deviation: VTE: Venous Thromboembolism.

Author	Study design	Mean age (years)	Number of patients	Males N, (%)	Arterial hypertension N, (%)	Diabetes N, (%)	Active cancer N, (%)	Cerebrovascular disease	Previous VTE	Setting		NOS
										ICU	*General wards*	
Lodigiani et al. [1]	Retrospective Single center	66 [55–75]	388	264 (58)	183 (47)	88 (23)	25 (6)	20 (5)	12 (3)	X	X	8
Poissy et al. [16]	Retrospective Single center	57	107	13/ 22** (59.1)	NR	NR	NR	NR	NR	X		7
Grillet et al. [17]	Retrospective Single center	66 (SD:13)	100	70 (70)	NR	20 (20)	20 (20)	NR	NR	X	X	7
Leonard-Lorant [8]	Retrospective Double-center	63.5	106	70 (66)	NR	NR	NR	NR	NR	X	X	7
Llitjos et al. [3]	Retrospective Double-center	68 [51.7–74.5]	26	20 (77)	22 (85)	NR	0	NR	1 (4)	X		7
Klok et al. [18]	Retrospective multicenter	64 (SD:12)	184	139 (76)	NR	NR	5 (3)	NR	NR	X		8
Thomas et al. [19]	Retrospective Single center	59 (SD:13)	63	44 (69)	NR	NR	NR	NR	NR	X	X	7
Middeldorp et al. [20]	Retrospective single center	61 (SD:14)	198	130 (66)	NR	NR	7 (3)	NR	11 (5)	X	X	8
Helms et al. [4]	Retropsective Multicenter	63 [53–71]	150	122 (81)	NR	30 (20)	9 (6)	72 (48)	8 (5)	X		8
Galeano-Valle et al. [21]	Prospective Single center	64.3 (SD:14.4)	24	14 (58.)	NR	NR	1 (4)	NR	NR		X	8
Bompard et al. [12]	Retrospective Double center	64 [64–76]	135	94 (70)	NR	NR	NR	NR	NR	X *		7
Soumagne et al. [22]	Retrospective Multicenter	63.5 (SD:10.1)	375	288 (77)	216 (58)	99 (26)	44 (12)	NR	NR	X		7
Freund et al. [23]	Retrospective Multicenter	61.0 (SD: 19)	3253	1558 (47.8)	1294 (40)	NR	442 (13.5)	NR	385 (11.8)		X°	7
Chen et al. [24]	Retrospective Single center	65 [56.5–70]	25	15 (60)	10 (40)	5 (20.0)	0	NR	NR		X	7
Longhcamp et al. [25]	Retrospective Single center	68 (SD: 11)	25	16 (64)	10 (40)	1 (4)	2 (8)	NR	0	X		6
Whyte et al. [26]	Retrospective Single center	61.5	214	129 (60.2)	NR	NR	16 (7)	NR	21 (10)	X	X	7
Marone et al. [27]	Retrospective Single center	NR	101	NR	NR	NR	NR	NR	NR		X	5
Fauvel et al. [28]	Retrospective Multicenter	64 (SD:17)	1240	721 (58)	559 (45)	268 (22)	167 (13.5)	94 (8)	98 (8)	X	X	8
Van den Heuvel [29]	Retrospective Single center	63 [51–68]	51	41 (80)	21 (41)	9 (18)	NR	2 (4)	NR		X	6
Mestre-Gomez et al. [30]	Retrospective Single center	65 [56–73]	29	21 (72)	12 (41)	3 (10.0)	5 (17)	1 (3)	1 (3.4)		X	7
van Dam et al. [31]	Retrospective Single center	63 (SD:6.4)	23	16 (70)	NR	NR	1 (4)	NR	1 (4)		X	7
Gervaise et al. [32]	Retrospective Single center	62.3 (SD:17.8)	72	54 (75)	NR	NR	NR	NR	NR		X	6
Trimaille et al. [33]	Retrospective Single center	62.2 (SD:17.0)	289	171 (59)	132 (46)	59 (20)	8 (3)	NR	28 (10)		X	8

* Only ICU patients were considered in the analysis since some cases of acute pulmonary embolism in non-ICU setting were also observed in outpatients.
** Referred to patients with acute Pulmonary embolism.° Emergency department (ED).

Our results have several implications for clinical practice. First, the high rate of acute PE in COVID-19 patients makes it urgent to establish the optimal antithrombotic regimen that may minimize the risk of thromboembolic events in these patients. In this regard, recent analyses and perspectives have proposed different therapeutic and prophylactic regimens but the debate is still ongoing [40,41]. Second, it appears clear that the diagnosis of acute PE is largely underestimated in COVID-19 patients. Indeed, only one third of patients underwent CTPA for diagnostic purposes. Yet, recent autoptic studies performed in COVID-19 patients have demonstrated the presence of arterial emboli involving both major pulmonary arteries and microthrombi involving the more distal arterial vessels [42-44]. Indeed, these two scenarios may coexist: local "immunothrombosis" triggered by the viral infection and "classic" venous thromboembolism caused by major transient provoking risk factors, including bed rest, the presence of catheters, 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. In this regard, both cytokine storm and/or macrophage activation syndrome (MAS) could trigger the expression of active tissue factor (TF) within the lungs, further activating the coagulation cascade [45]. It remains to be elucidated whether "immunothrombosis" can be prevented by standard thromboprophylaxis and can be cured by available anticoagulant regiments.

During the current COVID-19 pandemic, the traditional diagnostic algorithms have been frequently overturned to limit the risk of infection

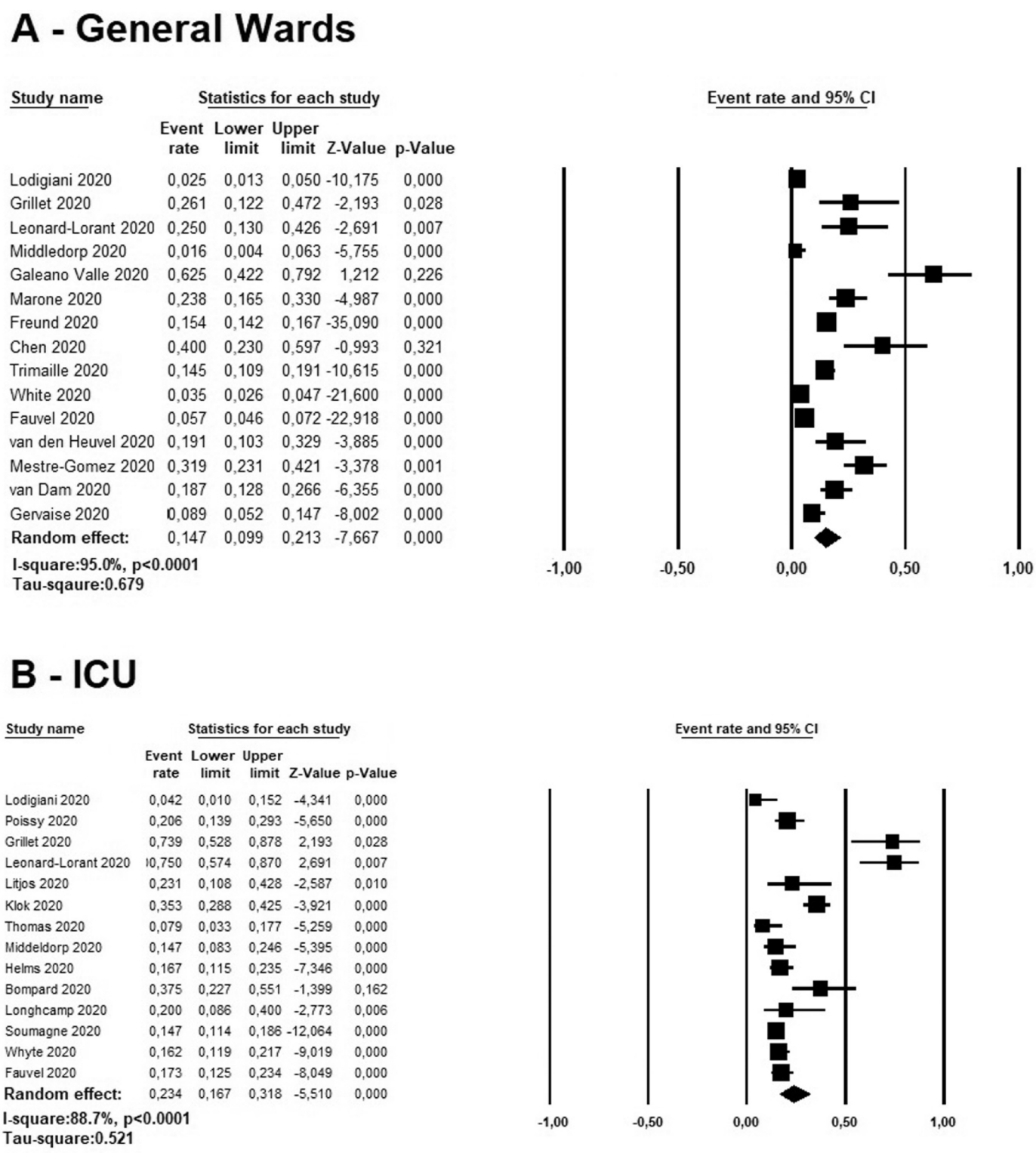

Fig. 2. Forest plots investigating the pooled incidence of acute pulmonary embolism in COVID-19 patients hospitalized in ICU (A) and in general wards (B).

for both operators and outpatients, limiting the execution of radiological examinations to minimize intrahospital transfers [46]. Indeed, there are obvious difficulties in perform CTPA in mechanical ventilated patients, especially when it requires pronation. Some of the reviewed studies evidenced that CTPA was performed in the event of further clinical and/or respiratory deterioration in ICU patients [3,12]. To reduce the burden of acute PE in these patients it seems essential to promote serial assessment using bedside transthoracic echocardiographic (TTE), electrocardiograms, assessment of myocardial injuries biomarkers [47,48] and compression ultrasonography (CUS), which may detect early, indirect signs that raise the suspicion of acute PE. A low threshold to suspect PE appears reasonable in this setting. At the same time, separate intra-hospital paths for the transfer of patients to radiological wards would permit the diagnosis of acute PE while minimizing the risk of infection.

A multinational registry, the COVID-19 Registry on Thrombosis and

Table 2
Anatomical sites of acute pulmonary embolism and percentages of imaging assessment performed to assess pulmonary thromboembolic events.NR not reported; NA: not applicable (retrospective studies); CTPA: Computed tomography pulmonary angiography; CUS: Compression ultrasonography. Follow-up was available only in prospective studies but one of this did not reported the length [21].

Author	Imaging techniques	Thromboprophylaxis	DVT	Follow-up	Sites of intraluminal pulmonary arterial filling defects				Imaging test performed (CTPA)
					Main (%)	Lobar (%)	Segmental (%)	Subsegmental (%)	(%)
Lodigiani et al. [1]	CTPA Two point CUS in ICU Whole leg ultrasound in general wards	Enoxaparin or Nadroparin NR for PE patients (only reported 100% of ICU patients)	PE ± DVT and isolated DVT reported separately	NA	NR		30.0	10.0	33
Poissy et al. [16]	CTPA	LWMH or UFH In 20/22 patients NR for PE patients	3/22 (13.6)	NA	10.0 * 40.0**		55.0	NR	31.8
Grillet et al. [17]	CTPA	NR	NR for PE patients	NA	0	43.4	100	0	35.7
Leonard-Lorant [8]	CTPA	LMWH 25/32 (78%)	NR for PE patients	NA	21.8	34.3	28.1	15.6	63.0
Llijtos et al. [3]	CTPA (in 4 patients) TEE (in 2 patients) Limb ultrasound	8 (31%) prophylactic anticoagulation 18 (69%) therapeutic anticoagulation NR for PE patients	NR for PE patients	NA	NR	NR	NR	NR	NR
Klok et al. [18]	CTPA Limb Ultrasound	Nadroparin in all patients with different regimens	NR for PE patients	NA	70.7			29.2	NR
Thomas et al. [19]	CTPA Limb Ultrasound	Prophylactic dalteparin in all patients NR for PE patients	NR for PE patients	NA	20	0	60.0	20	17.4
Middeldorp et al. [20]	CTPA Limb ultrasound	Thromboprophylaxis with nadroparin in 167 patients (84%) 19 patients (9.6%) continued therapeutic anticoagulation	Defined as PE ± DVT	17	7.6		76.9	15.3	NR
Helms et al. [4]	CTPA	LMWH or UFH Prophylactic dose 105 (70) Therapeutic dose 45 (60)	NR for PE patients	7	37.5	33.3	20.8	12.5	NR
Galeano-Valle et al. [21]	CTPA CUS	Enoxaparin or Bemiparin In 19/24 patients	4/11 (36.3)	NR	13.3	46.6	86.6	46.6	NR
Bompard et al. [12]	CTPA	Enoxaparin in all patients at prophylactic dose	NR for PE patients	26	31.2		65.2	12.5	53 °
Soumagne et al. [22]	CTPA	NR	35 (9.3)	NR	NR		NR	NR	14.6
Freund et al. [23]	CTPA	NR	101 (11)	NR	NR		NR	NR	15
Chen et al. [24]	CTPA	NR	1 (4)	NR	0	25 (100)	25 (100)	0	100
Longhcamp et al. [25]	CTPA	Intravenous heparin infusion or enoxaparin	6 (24)		0	3 (60)	2 (40)	0	28
Whyte et al. [26]	CTPA	Enoxaparing or UFH	7 (8.7)	NR	3 (3.7)	NR	28 (35)	13 (16.2)	14.4
Marone et al. [27]	CTPA CUS	LMWH	8 (33.3)	10	NR	NR	NR	NR	NR
Fauvel et al. [28]	CTPA	LMWH 738 (63.0)	18 (1.5)	NR	NR	NR	NR	NR	43.0
Van den Heuvel [29]	CTPA	NR	NR	NR	NR	NR	NR	NR	92
Mestre-Gomez et al. [30]	CTPA	LMWH 23 (79.3)	2 (6.9)	NR	9 (31)		20 (69)		NR
van Dam et al. [31]	CTPA	(100) Not specified the drug	0	NR	4 (17)		16 (70)	3 (13)	NR
Gervaise et al. [32]	CTPA	NR	NR	NR	2 (15)	4 (30)	7 (55)	0	49.3

(*continued on next page*)

Table 2 (*continued*)

Author	Imaging techniques	Thromboprophylaxis	DVT	Follow-up	Sites of intraluminal pulmonary arterial filling defects				Imaging test performed (CTPA)
Trimaille et al. [33]	CTPA	Enoxaparin	12 (24.5)	NR	NR	NR	NR	NR	34.6

* Defined as proximal;.
** Defined as bilateral. °Performed due to clinical deterioration.

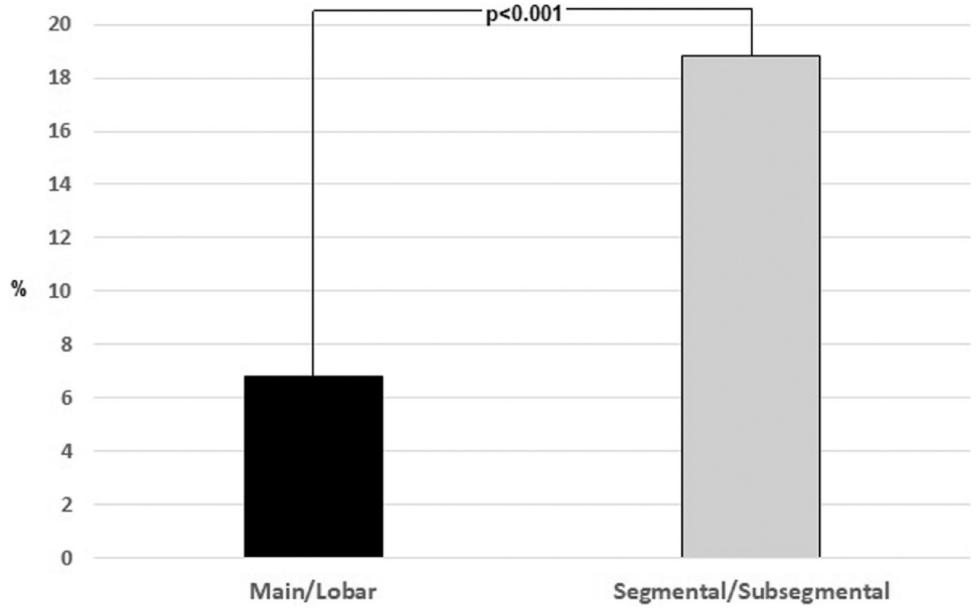

Fig. 3. Comparison of the proximal and distal distribution of intraluminal pulmonary arterial filling defects.

Thromboembolic complications (CORE-THROMBOSIS), is recruiting to provide representative data on the magnitude of the problem and enable us to formulate robust hypotheses to be tested in future trials [49].

4.1. Limitations

Our study has several limitations related to the observational nature of the studies reviewed and their own limitations with all inherited biases. In particular, potential underestimation could derive from detection bias if PE was not searched systematically or suspected based on systematic criteria, and CTPA may only have been carried out in patients with a clinical condition severe enough to raise the suspicion that other factors than the infection were at play. Sampling bias by the competing risk of death may also have led to underestimation of the real cumulative incidence of PE. At the same manner, we cannot assess if an adequate prophylactic anticoagulation was consistently administered in each study because these data were not systematically provided in the review investigations. Moreover, the hospitalization length can represent another potential source of bias since is strictly related immobilization [50]. This late aspect could explain the higher pooled cumulative in-hospital PE incidence in ICUs compared to general wards since ICU hospitalization, and immobilization, is generally longer. Few investigations on the COVID-19 infection have analysed the incidence of acute PE as a complication of COVID-19 infection, limiting the number of the studies included into the meta-analysis and the corresponding number of patients.

5. Conclusions

The pooled incidence of acute PE among COVID-19 patients was higher in ICU patients compared with patients hospitalized in general wards. Available data may underestimate the real incidence of acute PE as a complication of COVID-19 infection. A clinical and radiological distinction between acute PE and local “immunothrombosis” is impossible based on the available data and its therapeutic consequences remain to be investigated. Appropriate diagnostic strategies must be promoted to enhance the diagnosis of acute PE in these patients to reduce the mortality rate [51].

Declaration of Competing Interest

S.B. reports personal fees from Biocompatibles Group UK and Bayer HealthCare, non-financial support from Bayer HealthCare and Daiichi Sankyo, outside the submitted work.

S.V.K. reports grants and non-financial support from Bayer AG; grants and personal fees from Boehringer Ingelheim, personal fees from Bayer AG, grants and personal fees from Actelion, grants and personal fees from Daiichi-Sankyo, grants and personal fees from Biocompatibles Group UK, personal fees from Pfizer—Bristol-Myers Squibb, grants and personal fees from MSD, outside the submitted work

The other authors have no conflicts of interest to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2020.09.006.

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