

COVID-19 patients with acute pulmonary embolism have a higher mortality risk: systematic review and meta-analysis based on Italian cohorts

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Background Acute pulmonary embolism has been recognized as a frequent complication of COVID-19 infection influencing the clinical course and outcomes of these patients.

Objectives We performed a systematic review and meta-analysis to evaluate the mortality risk in COVID-19 Italian patients complicated by acute pulmonary embolism in the short-term period.

Methods The study was performed in accordance with the Preferred Report Items for Systematic Reviews and Meta-analyses guidelines. PubMed-MEDLINE and Scopus databases were systematically searched for articles, published in the English language and enrolling Italian cohorts with confirmed COVID-19 infection from inception through 20 October 2021. Mortality risk data were pooled using the Mantel–Haenszel random effects models with odds ratio as the effect measure with 95% confidence interval. Heterogeneity among studies was assessed using Higgins and Thomson I^2 statistic.

Results Eight investigations enrolling 1.681 patients (mean age 64.9 years, 1125 males) met the inclusion criteria and were considered for the analysis. A random-effect model showed that acute pulmonary embolism was present in 19.0% of Italian patients with COVID-19 infection. Moreover,

these patients were at higher mortality risk compared with those without (odds ratio: 1.76, 95% confidence interval: 1.26–2.47, $P=0.001$, $I^2=0\%$). Sensitivity analysis confirmed yielded results.

Conclusion In Italian patients with COVID-19 infection, acute pulmonary embolism was present in about one out of five and significantly associated with a higher mortality risk in the short-term period. The identification of acute pulmonary embolism in these patients remains critical to promptly identify vulnerable populations who would require prioritization in treatment and prevention and close monitoring.

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Introduction

Italy was the first country in Europe to be hit hard by the coronavirus, with more than 4.7 million cases and 132 000 deaths since the beginning of the pandemic. Acute pulmonary embolism has been recognized as a frequent complication of infection,¹ influencing the clinical course and outcomes of these patients.^{2,3} Intriguingly, a recent meta-analysis based on international investigations has reported no significant correlation between pulmonary embolism and mortality in COVID-19 patients.⁴ However, recent randomized controlled trials have demonstrated that thromboprophylaxis with therapeutic-dose low-molecular-weight heparin reduces the incidence of major thromboembolism and/or death in the same subjects.^{5,6} The aim of the present article is to perform a systematic review and meta-analysis to evaluate the mortality risk in COVID-19 Italian patients complicated by acute pulmonary embolism in the short-term period.

Materials and methods

Study design and eligibility criteria

The study was performed in accordance with the Preferred Report Items for Systematic Reviews and Meta-analyses guidelines.⁷ For this purpose, PubMed-MEDLINE and Scopus databases were systematically searched for articles, published in the English language and enrolling Italian cohorts of COVID-19 patients from inception through 20 October 2021, using the following Medical Subject Heading terms: ‘COVID-19’ AND ‘Pulmonary Embolism’ OR ‘Venous Thromboembolism’. Ethical approval and informed consent were not required as the study did not directly enrol human subjects.

Study selection and inclusion criteria

The selection of studies to be included in our analysis was independently conducted by two authors (M.Z. and G.Z.) in a blinded fashion. Any discrepancies in study selection

were resolved by consulting a third author (L.R.). Inclusion criteria were studies enrolling subjects with a confirmed diagnosis of COVID-19; based on Italian cohorts; stratifying the population as patients with and without COVID-19 infection; providing data on the short-term mortality (in hospital or 30-day mortality). Conversely, randomized controlled trials, case reports, review articles, editorials/letters, case series with fewer than 10 participants, international multicentric studies including as a part of the entire sample also Italian patients and studies including duplicate populations, if any, were excluded. Moreover, references from the included studies were screened to potentially identify other investigations meeting the inclusion criteria.

Data extraction and quality assessment

Data were independently extracted by two authors (G.R. and L.Q.) in a blinded fashion. Also in this case, any discrepancies were resolved by consulting a third author (L.R.). For all investigations included in the study we extracted the type of investigation, sample size, number of acute pulmonary embolism events, mortality rate, males percentage, mean age, presence of pulmonary embolism risk factors (such as cancer, obesity and previous venous thromboembolic events), concomitant comorbidities already associated with a poor outcome in COVID-19 patients including arterial hypertension⁸ and diabetes mellitus⁹ and administration of prophylactic or therapeutic anticoagulation treatments. The quality of the included studies was graded using the Newcastle–Ottawa quality assessment scale.¹⁰

Data synthesis and analysis

Continuous variables were expressed as mean \pm SD or as a mean with relative interquartile range while categorical variables were presented as numbers and relative percentages. The cumulative incidence of acute pulmonary embolism was defined and calculated as the ratio between COVID-19 patients experiencing pulmonary embolism (n) and the number of patients enrolled in each study (N). Mortality risk data were pooled using the Mantel–Haenszel random effects models with odds ratio (OR) as the effect measure with 95% confidence interval (CI). Heterogeneity among studies was assessed using the Higgins and Thomson I^2 statistic where I^2 values correspond to the following levels of heterogeneity: low (<25%), moderate (25%–75%) and high (>75%). The presence of potential publication bias was verified by visual inspection of the funnel plot. Due to the low number of the included studies (<10), small-study bias was not examined as our analysis was underpowered to detect such bias. However, a predefined sensitivity analysis (leave-one-out analysis) was performed by removing one study at a time, to evaluate the stability of our results regarding the mortality risk. All meta-analyses were conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, Tampa, Florida, USA).

Results

Search results study characteristics

Initial search resulted in 4951 articles. A total of 3623 articles were retrieved after excluding duplicates. The initial screening excluded 2248 articles because they did not meet inclusion criteria, leaving 1375 articles to assess for eligibility. Subsequently, after evaluation of the full-text articles, 1367 were excluded and 8 investigations met the inclusion criteria (Fig. 1).^{11–18}

Study characteristics

Overall, 1681 Italian patients with a confirmed diagnosis of COVID-19 infection (mean age 64.9 years old, 1125 males) were included in the analysis. The general characteristics of patients enrolled are shown in Table 1. In all patients, the diagnosis of acute pulmonary embolism was performed by using computed tomography angiography. The mortality rate and incidence of acute pulmonary embolism were 19.8% ($n = 334$) and 19.0% ($n = 320$), respectively.^{11–18} Despite concomitant comorbidities not being systematically evaluated by all the investigations, arterial hypertension and diabetes mellitus were the most common. Data regarding the administration of prophylactic anticoagulation, provided by four studies ($n = 1221$),^{12,14,17,18} showed that this anticoagulant regimen was used in 46.0% of cases ($n = 562$). Conversely, only two investigations ($n = 308$) provided data regarding the use of therapeutic anticoagulant treatment which was administered in 15.2% of patients ($n = 47$).^{12,14}

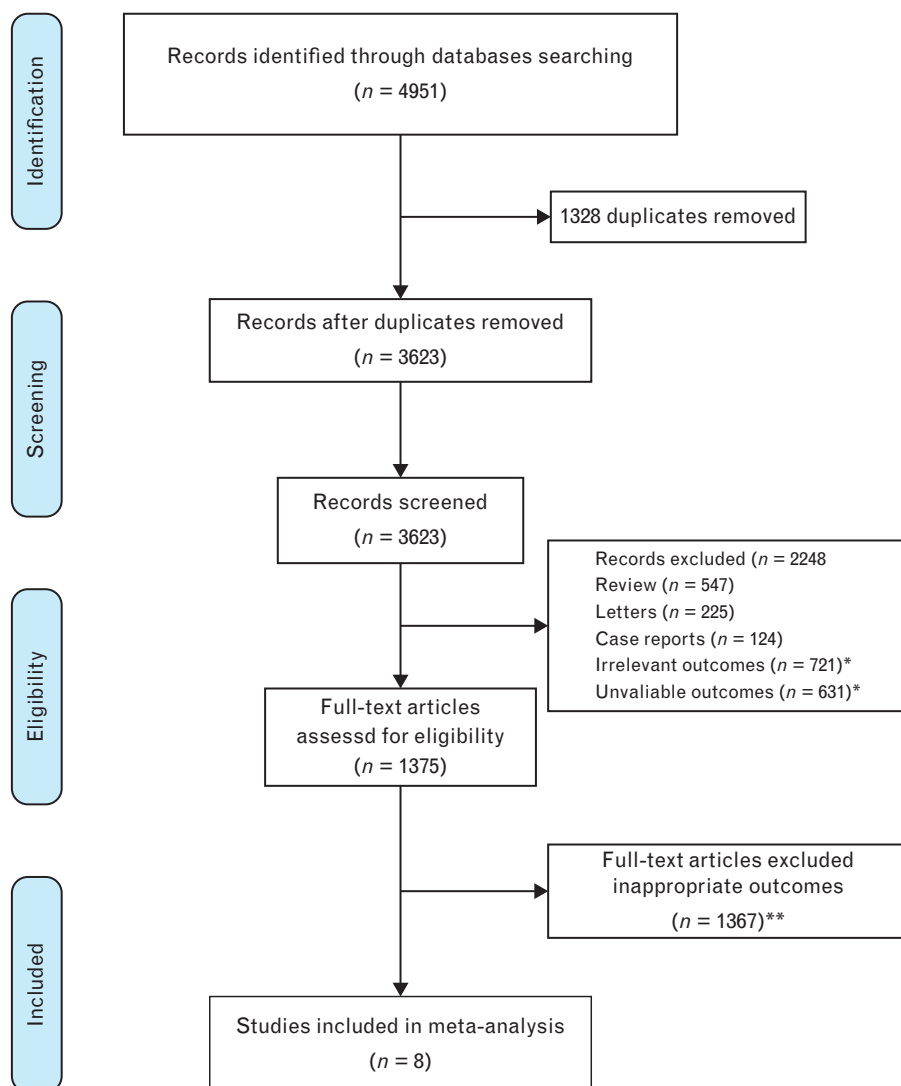
Mortality risk in COVID-19 patients with acute pulmonary embolism

On pooled analysis, patients with acute pulmonary embolism showed a significantly higher mortality risk in the short-term period (OR: 1.76, 95% CI: 1.26–2.47, $P = 0.001$, $I^2 = 0\%$) (Fig. 1, panel a).^{11–18} The visual inspection of the relative funnel plot did not reveal significant evidence of publication bias (Fig. 2, panel b). To evaluate the robustness of the association results, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time and recalculating the summary OR. The summary ORs remained stable (ranging between OR: 1.60, 95% CI: 1.10–2.32, $P = 0.001$ and OR: 1.85, 95% CI: 1.32–2.60, $P < 0.001$), indicating that our results were not driven by any single study.

Discussion

The results of present analysis demonstrated that Italian subjects with COVID-19 infection and concomitant acute pulmonary embolism have a higher mortality risk in the short-term period. Specifically, an additional 76% risk of death was observed in COVID-19 pulmonary embolism patients compared with those without.^{11–18} Our findings contradict those presented by Gomez *et al.*,⁴ who evidenced a comparable risk of mortality between pulmonary embolism and nonpulmonary embolism patients. More precisely, the authors presented their

Fig. 1



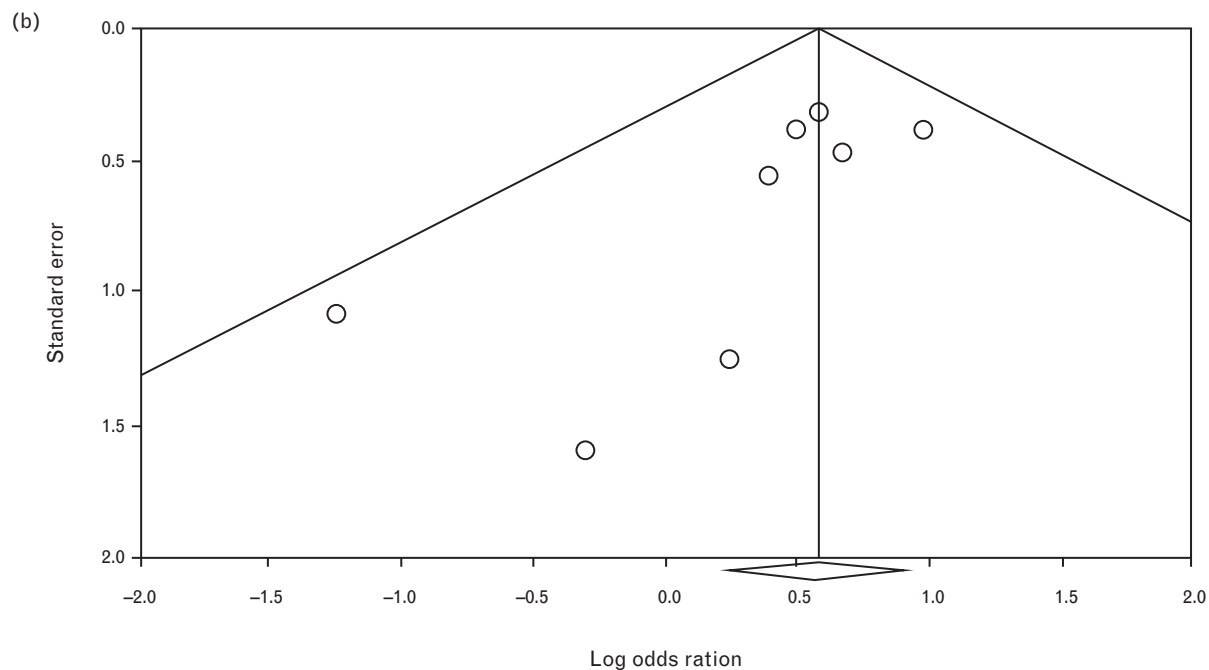
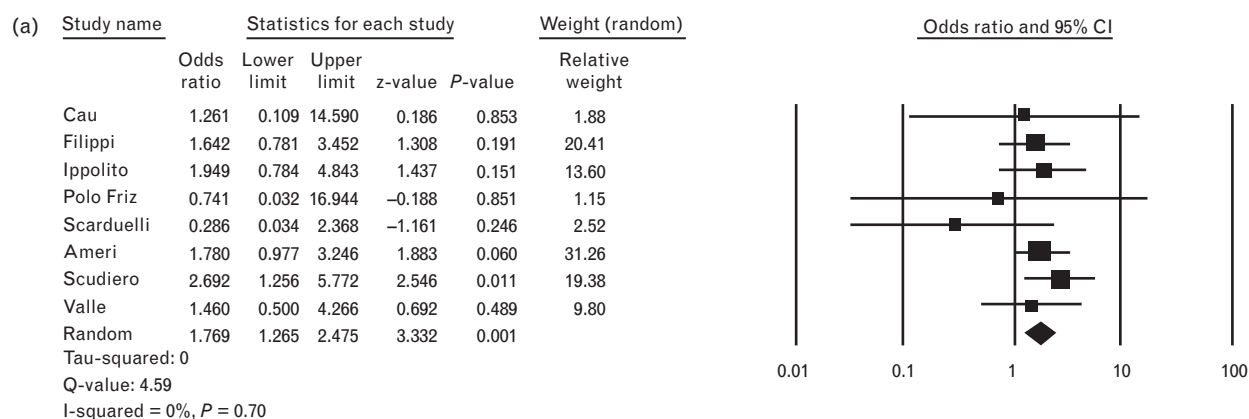
Preferred Report Items for Systematic Reviews and Meta-analyses flowchart. *Articles excluded because not provided mortality outcomes; **Articles excluded because not based on Italian cohorts.

Table 1 General characteristics of the population enrolled

Author	Type	Number of pts, N	PE, n	Mortality, N (%)	Males, N (%)	Mean age, years (IQR)	Cancer, N, (%)	Obesity, n (%)	HT, N (%)	DM, N (%)	Previous VTE, N (%)	Anticoagulation, N (%)	NOS
Cau <i>et al.</i> ¹¹	Retro S	84	26	3 (3.5)	57 (68.0)	60.4 (16.0)	8 (9.0)	NR	45 (53.0)	25 (30.0)	NR	NR	7
Filippi <i>et al.</i> ¹²	Retro S	267	50	47 (17.6)	172 (64.4)	69	17 (6.3)	48 (17.9)	NR	NR	8 (2.9)	P: 192 (71.9) T: 18 (6.7)	8
Ippolito <i>et al.</i> ¹³	Retro S	170	76	22 (12.9)	116 (68.2)	63 (12.0)	NR	NR	NR	NR	NR	NR	6
Polo Friz <i>et al.</i> ¹⁴	Retro S	41	8	2 (4.8)	11 (26.8)	71.7 (63–76.2)	3 (7.2)	NR	29 (70.7)	11 (26.8)	NR	P: 4 (9.7) T: 29 (70.7)	7
Scarduelli <i>et al.</i> ¹⁵	Retro S	92	11	11 (11.9)	71 (77.1)	58 (11)	NR	42 (45.0)	43 (46.0)	18 (19.0)	NR	NR	7
Ameri <i>et al.</i> ¹⁶	Retro Multi	689	52	164 (23.8)	487 (69.4)	67.3 (13.2)	NR	NR	398 (56.9)	157 (23.0)	NR	P: 185 (26.8)	7
Scudiero <i>et al.</i> ¹⁷	Retro Multi	224	32	68 (30.3)	127 (62.0)	69 (14.0)	27 (12.0)	NR	137 (61.0)	63 (28.0)	NR	P: 181 (81.0)	7
Valle <i>et al.</i> ¹⁸	Retro S	114	65	17 (14.9)	84 (73.7)	61 (51.2–66)	42 (36.8)	13 (11.4)	41 (35.9)	17 (14.9)	NR	NR	6

DM, diabetes mellitus; HT, arterial hypertension; IQR, interquartile range; NOS, Newcastle–Ottawa quality assessment scale; NR, not reported; P, prophylactic anticoagulation; PE, pulmonary embolism; pts, patients; T, therapeutic anticoagulation; VTE, venous thromboembolism.

Fig. 2



(a) Forest plot evaluating the mortality risk in COVID-19 patients with acute pulmonary embolism using a random-effect model. (b) Funnel plot for the mortality risk in COVID-19 patients with acute pulmonary embolism using a random-effect model.

results into a meta-analysis based on international studies; however, they did not perform any subanalysis for different countries. As known, Italy was the first country outside China to experience the impact of the COVID-19 pandemic. Therefore, we decided to investigate the impact of acute pulmonary embolism on Italian COVID-19 patients since our country has been hit hard by the pandemic, especially during the first phase. Moreover, considering that pulmonary embolism, and more in general COVID-19 complications, largely depend on the presence of comorbidities as well as the age of patients, it would be of interest to investigate the prognostic role of

thromboembolic events in such a scenario being that Italy is one of the oldest European countries with patients having a high prevalence of comorbidities.

The scant knowledge of underlying pathophysiological mechanisms and potential supportive treatment able to reduce the onset of complications and mortality risk in COVID-19 patients were largely unknown, especially during the first pandemic wave. These aspects may have led to higher complication rates as well as associated mortality events. However, also the demographical features of the population and the prevalence of concomitant

comorbidities may have influenced the onset of thromboembolic complications and relative outcomes, especially in patients with previous cardiovascular disease.^{19–24} Indeed, Italian mortality data demonstrated that there was a strong geographical pattern, mainly involving the Italian northern regions (Lombardy, Veneto and Emilia-Romagna) as well as age and sex distribution, being that older males were more frequently infected and died.^{25,26} Intriguingly, these issues have been also associated, *per se*, with a higher mortality risk in COVID-19 patients with acute pulmonary embolism and reflect the main characteristic of the population analysed. In fact, older COVID-19 males are at higher risk of acute pulmonary embolism and mortality due to the underlying infection.^{4,27,28} On the contrary, the revised investigations were conducted only during the first phase of the pandemic, in which the scant use of adequate anticoagulant treatments may have also contributed to the higher mortality risk in Italian COVID-19 patients with concomitant pulmonary embolism, as demonstrated by our results. Our findings confirm the results of several recent investigations which demonstrated that the clinical outcomes in patients with SARS-CoV-2 infection are closely related to the burden of associated cardiovascular comorbidities and complications during the infection.^{29–32} Understanding the risk factors associated with a poor outcome in these patients remains critical to promptly identify vulnerable populations who would require prioritization in treatment and prevention and close monitoring if infected.

Limitations

Our study has several limitations related to the design of the studies reviewed with all inherited biases and the numbers of investigations on the issue. In fact, a limited number of Italian studies have analysed the relationship between acute pulmonary embolism and mortality risk in COVID-19 patients, partially limiting our results and conclusions. However, the absence of heterogeneity confirmed the robustness of our findings. Moreover, we cannot assess the timing of acute pulmonary embolism onset, diagnosis and anticoagulant regimen used; these issues may have significantly influenced the incidence of acute pulmonary embolism and therefore the related mortality.

Conclusion

In Italian COVID-19 patients, acute pulmonary embolism was present in one patient out of four and significantly associated with a higher mortality risk in the short-term period. The prompt identification of acute pulmonary embolism in these patients remains critical to promptly identify vulnerable populations who would require prioritization in treatment and prevention and close monitoring.

Supplementary File 1. PRISMA checklist, <http://links.lww.com/JCM/A479>.

Conflicts of interest

There are no conflicts of interest.

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