SYSTEMATIC REVIEW

Incidence of acute pulmonary embolism among patients hospitalized with COVID-19: a systematic review and meta-analysis [version 1; peer review: 1 not approved]

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a global pandemic, which is associated with venous thromboembolism and pulmonary embolism (PE). This study aimed to estimate the pooled incidence of PE among patients hospitalized with COVID-19 within the published literature.

Methods: This systematic review and meta-analysis was performed according to PRISMA guidelines. An electronic search using MEDLINE /PubMed, ScienceDirect, Cochrane, and OpenGray databases was conducted May 19th, 2020. Search terms included "COVID 19", "SARS-CoV-2", "coronavirus disease 2019", "2019-nCoV", "Wuhan coronavirus", "Pulmonary embolism", "pulmonary thromboembolism", "Pulmonary embol*", "pulmonary thrombo*" and "PE". Eligible studies

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included sufficient data to calculate the incidence of PE diagnosed during hospitalization in patients with COVID-19. Case reports were excluded. Quality was assessed using the Newcastle-Ottawa scale (observational cohort and case-control), AXIS tool (cross-sectional), and quality assessment tool (case series). Demographics and PE incidence data were extracted from the included studies and analyzed with R language. The pooled incidence of PE in patients hospitalized with COVID-19 was calculated.

Results: The database search identified 128 records. Ten observational studies were eligible and were included in the meta-analysis with a total of 1722 patients (mean age= 63.36). The pooled PE incidence in patients hospitalized with COVID-19 was 17% (95% CI: 0.1-0.26). There was a high degree of study heterogeneity ($I^2 = 94\%$, $p < 0.01$).

Conclusion: The pooled PE incidence in patients hospitalized with COVID-19 is 17%. This increased incidence is greater than that previously reported in the general population of non-COVID-19. Attention and further investigation of this risk is warranted.

Keywords

Pulmonary Embolism, Coronavirus, COVID-19, Venous thromboembolism, Incidence, Meta-analysis

This article is included in the **Emerging Diseases and Outbreaks** gateway.

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Introduction

In December 2019, pneumonia of unknown cause was detected in Wuhan, China¹. The causative agent was identified and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)². On March 11th, 2020, the World Health Organization characterized the coronavirus disease of 2019 (COVID-19) as a pandemic^{1,3}, resulting in 53,507,282 and 1,305,164 COVID-19-related cases and deaths, respectively, as of November 15th, 2020⁴. While COVID-19 is primarily a pulmonary disease, there are multiple other pathologic manifestations and complications, including pulmonary embolism (PE)⁵.

The relationship between COVID-19 and thromboembolism is becoming established in the literature⁵. Thromboembolism has been previously associated with zoonotic coronaviruses⁶ and may be attributed to several factors including; a hypercoagulable state associated with severe infection or inflammation⁷, COVID-19 associated hemostatic abnormalities^{8,9}, recumbence^{7,10–12}, and possible drug interactions between investigational COVID-19 therapies (Lopinavir/ritonavir) and antithrombotics⁵.

This systematic review and meta-analysis analyzed and estimated the pooled PE incidence from published literature of patients hospitalized with COVID-19 who developed PE.

Methods

This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline^{13,14}. Institutional review board approval was not required for this study.

Search strategy

A systematic literature search was performed on May 19th, 2020 using Medline/PubMed, Cochrane, OpenGrey, and ScienceDirect. PubMed, Cochrane, and OpenGrey were queried for the following strategy: (“COVID 19” OR “SARS-CoV-2” OR “coronavirus disease 2019” OR “2019-nCoV” OR “Wuhan coronavirus”) AND (“Pulmonary embolism” OR “pulmonary thromboembolism” OR “Pulmonary embol*” OR “pulmonary thrombo*” OR “PE”). ScienceDirect was queried using the same variables only without asterisks.

Duplicate citations and older versions of the same study population were removed. All included study bibliographies were screened for additional articles investigating PE in patients hospitalized with COVID-19. All eligible studies underwent full-text screening.

Eligibility criteria

Studies reporting data sufficient to estimate PE incidence of patients hospitalized with COVID-19 were included in the analysis. Only English and published studies were included. Studies with insufficient data, case reports, editorials, proposals, and abstracts without full-text were excluded. The title and abstract of retrieved articles were screened by two independent reviewers for potential inclusion. Any discrepancy between the reviewers was resolved by consensus with two additional reviewers.

Quality appraisal and data extraction

Appraisal of individual study quality was performed by two independent reviewers using the Newcastle–Ottawa scale, AXIS tool, and quality assessment tool for observational cohort and case-control, cross-sectional, and case series, respectively^{15–17}. Articles were deemed of good quality if they scored 50% or more using an arbitrary cut-off.

Information was sought from each included study are: characteristics of participants (including age, gender, BMI, D dimer of patient with COVID-19, and total patients in the study), summary about included studies (first author, country, year of publication, study period, study design, method of diagnosing COVID-19) and the main data for meta-analysis (total patients in each study i.e., sample size and number of patients developing PE from the total). The data was subsequently extracted by five independent reviewers utilizing Microsoft Excel® 2016 (Microsoft Corporation, Redmond, WA).

Analysis

Due to skewed proportions, the random effect model was used to pool the individual estimates through LOGIT transformation instead of double arcsine transformation to avoid a paradoxical effect upon back-transformation^{18,19}.

Statistical analysis was performed using R language v.4²⁰, using “meta” and “metafor” packages^{21–23}. Random effects models were utilized to accommodate for the heterogeneity in the reported pooled incidences. Statistical heterogeneity was estimated using I^2 statistics and further assessed using subgroup analysis, meta-regression, influence analysis, and Gosh analysis. Publication bias was evaluated by both the Egger test and funnel plot visual analysis.

Results

Study characteristics

The search yielded 81 and 47 records in both Medline/PubMed and ScienceDirect, respectively. No records were identified in OpenGrey and Cochrane databases. After eliminating duplicate data, 125 studies were included for abstract screening, of which 76 were excluded due to insufficient data. Full-text screening of the remaining 49 studies excluded 38 records with an agreement kappa of 0.813. Of the remaining studies, one scored <50% on the quality assessment tool, leaving ten studies for pooled analysis (Table 1). Nine studies were from Europe and one study was from North America (Table 1). Studies were divided into descriptive and analytic categories for subgroup analysis (Table 1). The reported PE incidence among patients hospitalized with COVID-19 in all included studies ranged from 3–35% (Table 2). Details of the selection process are summarized in (Figure 1).

Patients had a mean age of 63 years. The incidence of PE was noted to be higher in males (Table 3). The D-dimer levels were specified between PE group and non-PE group in only three studies, while the remaining either reported it improperly or had missing data (Table 3).

Table 1. Patient characteristics of the included studies.

First author	Publication year	Region	Country	Study period MM/DD/YYYY	Study design type	Design (analytic or descriptive)	Method of COVID-19 diagnosis
Lodigiani <i>et al.</i> , 2020 ²⁴	2020	Europe	Italy	02/13/2020 To 04/10/2020	Retrospective Cohort	Analytic	Laboratory
Middeldorp <i>et al.</i> , 2020 ²⁵	2020	Europe	Netherlands	03/02/2020 To 04/30/2020	Retrospective Cohort	Analytic	RT-PCR/ CT/ Clinical
Helms <i>et al.</i> , 2020 ²⁶	2020	Europe	France	03/03/2020 To 04/07/2020	Prospective Cohort	Analytic	RT-PCR
Bompard <i>et al.</i> , 2020 ²⁷	2020	Europe	France	03/01/2020 To 04/16/2020	Retrospective Cohort	Analytic	NA
Poyiadi <i>et al.</i> , 2020 ²⁸	2020	North America	Detroit	03/16/2020 To 04/18/2020	Case Control	Analytic	RT-PCR
Grillet <i>et al.</i> , 2020 ²⁹	2020	Europe	France	03/15/2020 To 04/14/2020	Retrospective Cross Sectional	Descriptive	RT-PCR / Strong Clinical Suspicion
Leonard-Lorant <i>et al.</i> , 2020 ³⁰	2020	Europe	France	03/01/2020 To 03/31/2020	Retrospective Cross Sectional	Descriptive	RT-PCR / CT and Clinical
Possy <i>et al.</i> , 2020 ³¹	2020	Europe	France	02/27/2020 To 04/09/2020	Case Series	Descriptive	PCR
Klok <i>et al.</i> , 2020 ³²	2020	Europe	Netherlands	03/07/2020 To 04/22/2020	Case Series	Descriptive	NA
Llitjos <i>et al.</i> , 2020 ³³	2020	Europe	France	03/19/2020 To 04/11/2020	Retrospective cross sectional	Descriptive	PCR

Table 2. Primary data for calculation of the incidence of patients hospitalized with COVID-19.

First author	Sample size	Number of CTPA	Number of PE	PE proportion
Lodigiani <i>et al.</i> , 2020 ²⁴	388	30	10	0.03
Middeldorp <i>et al.</i> , 2020 ²⁵	198	NA	13	0.07
Helms <i>et al.</i> , 2020 ²⁶	150	99	25	0.17
Bompard <i>et al.</i> , 2020 ²⁷	135	135	32	0.24
Poyiadi <i>et al.</i> , 2020 ²⁸	328	328	72	0.22
Grillet <i>et al.</i> , 2020 ²⁹	100	100	23	0.23
Leonard-Lorant <i>et al.</i> , 2020 ³⁰	106	106	32	0.30
Possy <i>et al.</i> , 2020 ³¹	107	34	22	0.21
Klok <i>et al.</i> , 2020 ³²	184	NA	65	0.35
Llitjos <i>et al.</i> , 2020 ³³	26	NA	6	0.23

PE: pulmonary embolism; CTPA: CT pulmonary angiography.

Though anatomical distribution of PE was mentioned in most studies (except Lorant *et al.* and Grillet *et al.*)^{29,30}, the clinical classification of PE into massive and sub-massive was not mentioned.

Meta-analysis

The pooled incidence of PE in hospitalized patients with COVID-19 was 17% (95% CI: 11-26%) (Figure 2). I^2 test revealed significant study heterogeneity ($I^2 = 94\%$, $p < 0.01$). The risk of

Figure 1. The study selection process depicted using the PRISMA flowchart.

publication bias was tested for by Egger test (t-value = -1.867, $p=0.0989$) and examined visually using a funnel plot (Figure 3).

Subgroup analysis

The pooled PE incidence was estimated at 11% (95% CI: 5-23%) and 27% (95% CI 22-34%) in the analytic and descriptive studies, respectively. Higher heterogeneity was detected among the analytic group ($I^2=95\%$, $p<0.01$), compared to the descriptive group ($I^2=48\%$, $p=0.05$) (Figure 4).

Meta-regression

When categorizing the included studies into analytic or descriptive, the meta-regression model showed that the study design was significantly associated with the difference in PE incidence ($p<0.05$) (Figure 5).

Discussion

PE is the most common thromboembolic complication occurring in patients with COVID-19^{24,30,32}. This systematic review and meta-analysis estimated a pooled PE incidence among patients hospitalized with COVID-19 at 17% (95% CI: 10-26%) (Figure 2)²⁴⁻³³. This pooled PE incidence is higher than the PE incidence of the general population, and most importantly, higher than that of hospitalized patients with other medical conditions³⁴⁻⁴⁰.

This reported PE incidence could represent an over or under estimation of the true incidence. The increasing knowledge of higher incidences of venous thromboembolism in patients with COVID-19 may have led to a selection bias due to lower threshold of CT pulmonary angiography (CTPA) utilization⁴¹.

Table 3. Characteristics of patients hospitalized with COVID-19 and those who developed pulmonary embolism (PE).

First author	Age of patients with PE (years)	Male patients with PE (n (%))	BMI of patients with PE (kg/m ²)	D-dimer of patients with PE	Age of total patients (years)	Male total patients (n (%))	BMI of total patients (kg/m ²)	D-dimer of total patients
Lodigiani <i>et al.</i> , 2020 ²⁴	Mean = 69.3	7 (70)	NA	Mean = 10669.9 ng/ml	Median (IQR)= 66 (55-75)	264 (68)	>30 =24.1%	NA
Middeldorp <i>et al.</i> , 2020 ²⁵	NA	NA	NA	NA	Mean±SD = 61±14	130 (66)	Median (IQR) = 27 (24-31)	Median (IQR)= 1.1 (0.7-2.3) mg/l
Helms <i>et al.</i> , 2020 ²⁶	Mean = 62	24 (96)	NA	NA	Median (IQR)= 63 (53-71)	122 (81.3)	NA	Median (IQR) = 2.27 (1.16-20) mg/l
Bompard <i>et al.</i> , 2020 ²⁷	Median (IQR) = 70 (59-77)	26 (81)	NA	Median (IQR) = 9841 (2921-10000) u/l	Median (IQR)= 64 (54-76)	94 (70)	NA	Median (IQR) = 1285 (891 - 2742) u/l*
Poyiadi <i>et al.</i> , 2020 ²⁸	Mean±SD = 59±15	35 (49)	42 (58%) >30	Mean±SD = 9.33±7 mg/ml	Mean = 61.3	150 (45.7)	155 (47.2%) >30	Mean±SD = 2.54±3.67 mg/ml*
Grillet <i>et al.</i> , 2020 ²⁹	Mean±SD = 67±11	21 (91)	NA	NA	Mean±SD = 66±13	70 (70)	NA	NA
Leonard-Lorant <i>et al.</i> , 2020 ³⁰	Mean±SD = 64±22	25 (78)	Median (IQR) = 27±8	Median (IQR) = 15385±14410ug/l	Mean = 63.3	70 (66)	Mean = 28.4	Mean±SD = 1940 ± 3060 ug/l*
Possy <i>et al.</i> , 2020 ³¹	Median (range) = 57 (29-80)	13 (59.1)	Median (range) = 30 (22-53)	NA	NA	NA	NA	NA
Klok <i>et al.</i> , 2020 ³²	NA	NA	NA	NA	Mean±SD= 64±12	139 (76)	NA	NA
Litjens <i>et al.</i> , 2020 ³³	NA	NA	NA	NA	Mean±SD= 68±11.5	20 (77)	NA	NA

*data in non-PE group

Figure 2. Forest plot of included studies and their pooled estimate.

Figure 3. Funnel plot for assessment of any potential publication bias.

An underestimation is known to occur in the general population for the diagnosis of PE related to the majority of massive PE being diagnosed on post-mortem examination. Similarly, patients with COVID-19 could be assumed to have a lower reported

incidence of PE diagnosis due to; limited CT scan availability, patients instability, concern over hospital exposure to others related to transportation, early hospital mortality and death outside of healthcare^{5,42-44}.

Figure 4. Forest plot of subgroup analysis.

Figure 5. Meta-regression plot showing both LOGIT and back-transformation.

Most of the patients included in this meta-analysis were males and aged sixty years and above. Not only was PE higher in elderly and males patients hospitalized with COVID-19, but also other COVID-19 related complications and death were seen more in this population^{45,46}. This observation is consistent with

the higher PE incidence across the elderly in the general population as well⁴⁷. Therefore, hospitalized male and elderly patients with COVID-19 could be at a higher risk of developing PE compared to their COVID-19-afflicted female and young counterparts, respectively.

To account for the variability of CTPA timing effect on PE incidence, a study assigned each patient with COVID-19 two time points in the CTPA and demonstrated a higher incidence at the later time point²⁷. Such an observation may help in interpreting the variation in PE incidence across different studies with similar population characteristics and may also highlight underestimation of PE incidence in population with single time CTPA.

PE mortality was reported in only 3 out of the 10 studies using different formats^{24,25,27,28,33}. Therefore, the estimated pooled mortality could not be calculated.

Strength, limitations, and recommendations

This study was designed and executed in accordance with PRISMA guidelines. The heterogenous severity of the included COVID-19 cohort included the complete spectrum of hospitalized patients with COVID-19. Therefore, this estimated incidence could apply to any hospitalized patients with COVID-19, regardless of disease acuity. However, these findings need to be interpreted in the context of some limitations. First, neither articles in non-indexed journals nor non-published papers were searched, which may have introduced some publication bias. Second, the inclusion of studies published only in English literature may have led to language bias. Third, the presence of a subpopulation in whom PE was suspected and CTPA could not be performed for various reasons, such as allergy to contrast material, and could result in skewed incidence. Fourth, both clinical indications for CTPA and PE classification or risk stratification were not specified in the different studies. Sixth, due to variability of the way of reporting specific data on some variables (d-dimer, mortality data), it was difficult to make meaningful predictions. Lastly, some relevant clinical and para-clinical variables were not mentioned.

Further research is warranted to accurately characterize the patients hospitalized with COVID-19 who develop PE in terms

of; risk factors profile, PE diagnostic indications, CTPA timing, PE prophylaxis and management, and PE pathogenesis.

Conclusion

This systematic review and meta-analysis reported a pooled PE incidence among patients hospitalized with COVID-19 at 17%, suggesting that almost in every five hospitalized patients with COVID-19, one may develop PE. This represents around a 243-fold increase in incidence when compared to the general population. Healthcare professionals should be aware of this observed increase in risk of PE incidence among patients hospitalized with COVID-19. Development of accurate and precise risk stratification scores and point of care biomarkers to guide prophylactic and therapeutic strategies in this vulnerable population are warranted.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Open Science Framework: Codes and PRISMA checklist, <https://doi.org/10.6084/m9.figshare.13347473.v2>⁴⁸.

This project contains the following extended data:

- Code for publishing plots (.R file).
- Code for meta-analysis (.R file).

Reporting guidelines

Open Science Framework: PRISMA checklist for 'Incidence of acute pulmonary embolism among patients hospitalized with COVID-19: a systematic review and meta-analysis', <https://doi.org/10.6084/m9.figshare.13347473.v2>⁴⁸.

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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This paper is too simple, especially the Results section focusing on the pooled incidence of PE. Data analysis should be expanded to explore the risk factors and impact of PE. Can the relationship between PE and COVID-19 severity be established? Additionally, it is suggested that several subgroups can be used to analyze the source of heterogeneity.

Some published papers regarding a similar topic should be included. The Results section of the Abstract could introduce more contents regarding the main results of the study, while the Methods section can be shortened.

The Introduction section says, "*In December 2019, pneumonia of unknown cause was detected in Wuhan, China*". Such words are not appropriate; the first case of COVID-19 is still unclear.

It is more appropriate to use MOOSE guidelines for a systematic review and meta-analysis of articles discussing the incidence.

Current research is not registered on PROSPERO.

The authors say, "*A systematic literature search was performed on May 19th, 2020*". This paper is a bit older. It should be updated and collect more new data.

The data analysis is a bit simple and the significance of the p value was not defined.

The research flow chart is not concise enough. What is the meaning of "*36 records with no sufficient*"?

The authors said "*Random effects models were utilized to accommodate for the heterogeneity in the reported pooled incidences*". However, they still introduced fixed-effect models in figures.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

No

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Systematic review and meta-analysis; Clinical studies

We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 09 Apr 2021

Hussein Ahmed, University of Khartoum, Khartoum, Sudan

Dear reviewer,

Thank you for your valuable comments, we did a systematic review and meta-analysis regarding the incidence of PE among patients hospitalized due to COVID-19.

Our ultimate aim is to calculate the pooled incidence of PE to quantify the importance of that deadly condition. when we did this review, it was the first review at that time, and so published papers regarding a similar topic were not included. The Introduction section we say, "*In December 2019, pneumonia of unknown cause was detected in Wuhan, China*". By this we mean as the WHO reported the first appearance of COVID-19 in China and not the first case of COVID-19.

It is an advantage but not necessary to register our research at PROSPERO. We have also corrected the missing word in the flowchart to be more concise and we removed the fixed effect model from the figures.

Competing Interests: No competing interests were disclosed.

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