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Letter: In reference to a recent article

Incidence of venous and arterial thromboembolic complications in COVID-19: A systematic review and meta-analysis

Running Head: Thromboembolic complications in COVID-19

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Figure [1]

To the Editors

Arterial thrombotic disease (atherosclerotic cardiovascular disease, CVD) and venous thromboembolism (VTE) (comprising of deep vein thrombosis (DVT) and pulmonary embolism (PE)), two distinct but closely related diseases,[1] constitute major public health problems and are associated with substantial morbidity, premature mortality, and high economic costs. The coronavirus disease 2019 (COVID-19) pandemic which is one of the most significant modern-day public health challenges, predominantly affects the respiratory system, causing severe pneumonia and respiratory distress syndrome. Emerging data suggests COVID-19 adversely affects multiple organs; gastrointestinal, liver, kidney, neurological and cardiac complications have been reported.[2-4] Apart from pre-existing comorbidities such as CVD, hypertension, chronic kidney disease, chronic liver disease and diabetes being linked to increased risk of severe illness or death;[5] some extrapulmonary complications of COVID-19 such as acute myocardial injury have been shown to be associated with fatal outcomes.[6] Recently, COVID-19 has been linked to venous and arterial thromboembolic disease (henceforth referred to as thromboembolic complications). Three recent most downloaded and key studies published in the journal reported a high incidence of thromboembolic complications in COVID-19 patients, particularly in those admitted to the intensive care unit (ICU).[7-9] Given the sparseness of the data and evolving nature of the disease, the thromboembolic complications of COVID-19 and their incidence is not clearly defined. There is a need for robust aggregation of data on thromboembolic complications of COVID-19, which will be of great value for policy makers, healthcare providers and clinicians to aid decision making and implementing more efficacious preventative strategies. In this context, we conducted a systematic review and meta-analysis to attempt to address the following questions: (i) what are the thromboembolic complications associated with COVID-19 and (ii) what is the incidence of these complications overall and in those who develop severe disease?

The review was conducted in accordance with PRISMA and MOOSE guidelines (**Supplementary Materials 1-2**). We searched MEDLINE and Embase from January 2020 to 6 August 2020 for published studies reporting on venous and arterial thromboembolic complications (e.g., VTE, PE, myocardial infarction (MI), acute coronary syndrome (ACS), ischemic stroke, disseminated intravascular coagulation (DIC)) in patients with COVID-19. Studies based on selected patients/populations (eg, cancer patients) were not included. Details of the search strategy are reported in **Supplementary Material 3**. The incidence of thromboembolic complications (estimated from the number of patients experiencing the specific complication

within period of follow-up (hospital stay)/total number of patients with COVID-19) across studies with their 95% confidence intervals (CIs) were pooled using Freeman-Tukey variance stabilising double arcsine transformation and random-effects models. STATA release MP 16 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

Thirty-five observational cohort studies comprising of 9,249 hospitalised patients with COVID-19 were eligible (**Table 1; Supplementary Materials 4-5**). Seven studies were based in China and France each, 6 each in Italy and USA, 4 in the UK, 2 in the Netherlands and one each in Germany, Spain, and Switzerland. The average age at baseline ranged from 53 to 71 years. Severe COVID-19 was defined as requiring Intensive Care Unit (ICU) care or admission and this was consistent across all studies.

Figure 1 portrays incidence of thromboembolic complications overall in COVID-19 patients over hospital stays/follow-up periods ranging from 2 to 30 days. The pooled incidence was 18.4% (12.0-25.7) for VTE (n=19 studies), 13.5% (8.4-19.5) for PE (n=22 studies) and 11.8% (7.1-17.4) for DVT (n=18 studies) (**Figure 1A**). The incidence of DVT subtypes are reported in **Supplementary Material 6**. The incidence of distal, bilateral, proximal, symptomatic and upper extremity DVT was 13.6% (2.6-31.0), 7.6% (4.9-10.9), 3.3% (1.2-6.2), 2.6% (0.5-5.9) and 1.7% (0.4-3.6) respectively. For PE subtypes, the incidence was 9.1% (5.0-14.3) for segmental PE, 7.5% (0.5-19.9) for central/lobar PE, 6.3% (2.3-11.8) for subsegmental PE, 4.1% (2.0-6.9) for main pulmonary artery PE and 1.9% (0.0-6.5) for multiple segmental PE (**Supplementary Material 7**).

Other thromboembolic complications are reported in **Figure 1B**. The incidence of the composite outcome of arterial and venous thromboembolic disease was 17.8% (9.9-27.4). The incidence of superficial vein thrombosis, DIC, ACS/MI, catheter-related thrombosis, ischemic stroke, overt DIC, systemic arterial embolism, mesenteric and limb ischemia was 7.7% (1.7-16.5), 5.6% (3.4-8.3), 3.3% (0.3-8.5), 2.4% (0.2-6.2), 1.8% (1.3-2.4), 1.7% (0.5-3.5), 1.6% (0.4-3.6), 1.4% (0.2-3.5) and 1.1% (0.1-3.0) respectively. Other outcomes reported were symptomatic VTE and portal vein thrombosis, but these were based on single reports (**Figure 1B**).

The incidence of thromboembolic complications in patients with severe COVID-19 are reported in **Supplementary Materials 8-11**. The pooled incidence for VTE, PE and DVT was 21.6% (14.3-29.8), 11.8% (6.4-18.5) and 18.2% (9.6-28.6) respectively (**Supplementary Material 8**). The incidence of distal, proximal

and upper extremity DVT was 21.5% (0.0-72.8), 7.8% (1.8-16.9) and 3.5% (1.2-6.9) respectively (**Supplementary Material 9**). For PE subtypes, the incidence was 7.7% (3.9-12.4) for segmental PE, 4.0% (0.7-9.3) for subsegmental PE, 2.8% (0.1-7.4) for central/lobar PE and 1.9% (0.0-6.5) for multiple segmental PE (**Supplementary Material 10**). The incidence of the composite outcome of arterial and venous thromboembolic disease, ACS/MI, ischemic stroke, catheter-related thrombosis, mesenteric and limb ischemia was 22.9% (14.5-32.4), 4.7% (0.0-14.6), 3.3% (2.5-4.2), 3.1% (0.8-6.5), 1.4% (0.2-3.5) and 1.1% (0.1-3.0) respectively (**Supplementary Material 11**).

Based on the most up-to-date published evidence on patients with COVID-19, there is a high incidence of thromboembolic complications in these patients (ranging from 7.2 to 40.8%), which appears to be driven by venous thromboembolic disease. These thromboembolic complications are remarkably high in COVID-19 infection despite the use of thromboprophylaxis in patients. The most frequently diagnosed venous thromboembolic complication in the overall population is PE, with segmental and central/lobar PE being more common than other subtypes. Furthermore, it appears the incidence of thromboembolic complications is substantially higher in severe COVID-19 disease compared to the overall population, with a higher incidence of DVT than PE. Though arterial thrombosis and VTE have historically been viewed as two distinct diseases with different pathophysiology, they appear to be closely related via some shared risk factors (obesity and smoking) and mechanistic pathways (such as coagulation, platelet activation and dyslipidaemia).[1] Though the mechanistic pathways are still not very clear, the predisposition to venous and arterial thromboembolism by COVID-19 especially in severe infection has been attributed to the overwhelming inflammatory response, hypoxia, DIC and immobilisation.[2] There is an on-going discussion that pulmonary thrombotic events in COVID-19 may not be due to emboli but rather as a result of in-situ pulmonary thrombosis.[10]

The high incidence of thromboembolic complications in COVID-19 patients is a big source of concern, especially given the fact that systemic thromboprophylactic agents were administered to patients. Furthermore, it has been acknowledged by some studies that the thromboembolic incidence estimates reported are actually underestimates.[7, 8] Aggressive monitoring of markers of thromboembolic complications such as D-dimer during admission, use of sensitive and specific VTE diagnostic tools and effective pharmacological thromboprophylaxis may be required in the management of patients with COVID-19. Given the bleeding risks

associated with anticoagulants, clinical decisions to initiate thromboprophylaxis should also be individualised and tailored to each patient.

There were some limitations in this study, but these were all inherent. These included the low methodological quality of some of the studies and small sample sizes; however, this was not unexpected given the urgency to understand the clinical course of COVID-19. Other limitations included some findings being based on single reports and the fact that some of the incidence data were under-reported due to inability to perform diagnostic imaging tests in all patients due to strict isolation procedures.

Aggregate analysis of the available literature suggests a high incidence of thromboembolic complications in patients hospitalised with COVID-19, particularly in those with severe disease. The incidence is higher for venous thromboembolic events compared to arterial thromboembolic complications. There is an urgent need for improved diagnostic strategies as well as determining the most effective thromboprophylactic agents and their optimal dosages to be used in these patients.

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Declarations of interest

None.

References

[1] A. Delluc, K. Lacut, M.A. Rodger, Arterial and venous thrombosis: What's the link? A narrative review, Thromb Res 191 (2020) 97-102.

[2] S.K. Kunutsor, J.A. Laukkanen, Cardiovascular complications in COVID-19: A systematic review and meta-analysis, J Infect (2020).

[3] S.K. Kunutsor, J.A. Laukkanen, Hepatic manifestations and complications of COVID-19: A systematic review and meta-analysis, J Infect (2020).

[4] S. Behzad, L. Aghaghazvini, A.R. Radmard, A. Gholamrezanezhad, Extrapulmonary manifestations of COVID-19: Radiologic and clinical overview, Clin Imaging 66 (2020) 35-41.

[5] Z. Zheng, F. Peng, B. Xu, J. Zhao, H. Liu, J. Peng, Q. Li, C. Jiang, Y. Zhou, S. Liu, C. Ye, P. Zhang, Y. Xing, H. Guo, W. Tang, Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis, J Infect (2020).

[6] T. Guo, Y. Fan, M. Chen, X. Wu, L. Zhang, T. He, H. Wang, J. Wan, X. Wang, Z. Lu, Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19), JAMA Cardiol (2020).

[7] F.A. Klok, M. Kruip, N.J.M. van der Meer, M.S. Arbous, D. Gommers, K.M. Kant, F.H.J. Kaptein, J. van Paassen, M.A.M. Stals, M.V. Huisman, H. Endeman, Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis, Thromb Res 191 (2020) 148-150.

[8] W. Thomas, J. Varley, A. Johnston, E. Symington, M. Robinson, K. Sheares, A. Lavinio, M. Besser, Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom, Thromb Res 191 (2020) 76-77.

[9] C. Lodigiani, G. Iapichino, L. Carenzo, M. Cecconi, P. Ferrazzi, T. Sebastian, N. Kucher, J.D. Studt, C. Sacco, B. Alexia, M.T. Sandri, S. Barco, C.-T.F. Humanitas, Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy, Thromb Res 191 (2020) 9-14.

[10] F. Al-Ani, S. Chehade, A. Lazo-Langner, Thrombosis risk associated with COVID-19 infection. A scoping review, Thromb Res 192 (2020) 152-160.

Figure legends

Fig. 1 (A) Incidence of venous thromboembolic complications in COVID-19 patients; (B) Incidence of other venous and arterial thromboembolic complications in COVID-19 patients

ACS, acute coronary syndrome; CI, confidence interval (bars); DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism; VTE, venous thromboembolism

Overt DIC was defined as International Society on Thrombosis and Haemostasis (ISTH) score ≥ 5

Composite outcome refers to the composite outcome of arterial and venous thromboembolic disease

SUPPLEMENTARY MATERIAL

Supplementary Material 1	PRISMA checklist
Supplementary Material 2	MOOSE checklist
Supplementary Material 3	MEDLINE literature search strategy
Supplementary Material 4	Selection of studies included in the meta-analysis
Supplementary Material 5	Reference list of included studies
Supplementary Material 6	Incidence of deep vein thrombosis subtypes in COVID-19 patients
Supplementary Material 7	Incidence of pulmonary embolism subtypes in COVID-19 patients
Supplementary Material 8	Incidence of venous thromboembolic complications in severe COVID-19 patients
Supplementary Material 9	Incidence of deep vein thrombosis subtypes in severe COVID-19 patients
Supplementary Material 10	Incidence of pulmonary embolism subtypes in severe COVID-19 patients
Supplementary Material 11	Incidence of other venous and arterial thromboembolic complications in severe COVID-19 patients

Supplementary Material 1: PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Methods
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Supplementary material 3
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results, Supplementary material 4
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Results, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Results
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results, Figure 1; Supplementary materials 6-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Not applicable
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Not applicable
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Discussion
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	Funding section

Supplementary Material 2. MOOSE checklist

Incidence of venous and arterial thromboembolic complications in COVID-19: A systematic review and meta-analysis

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	Thromboembolic manifestations of COVID-19 are not clearly defined.
√	Hypothesis statement	(i) What are the thromboembolic complications associated with COVID-19? and (ii) what is the incidence of these complications overall and in those who develop severe disease?
√	Description of study outcomes	Venous and arterial thromboembolic complications
√	Type of exposure	Incidence estimates
√	Type of study designs used	Observational cohort designs
√	Study population	Adult patients with COVID-19
Reporting of search strategy should include		
√	Qualifications of searchers	Setor K. Kunutsor, PhD
√	Search strategy, including time period included in the synthesis and keywords	Time period: from inception to 06 August 2020 The detailed search strategy can be found in Supplementary material 3
√	Databases and registries searched	MEDLINE and Embase
√	Search software used, name and version, including special features	OvidSP was used to search Embase and MEDLINE EndNote X9 used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies are available on request.
√	Method of addressing articles published in languages other than English	Not applicable
√	Method of handling abstracts and unpublished studies	Not applicable
√	Description of any contact with authors	None
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, and outcome.
√	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome. Sensitivity analyses by several quality indicators such as study size, duration of follow-up, and adjustment factors.
√	Assessment of heterogeneity	Results
√	Description of statistical methods in sufficient detail to be replicated	Described in methods section
√	Provision of appropriate tables and graphics	Table 1; Figure 1; Supplementary materials 6-11
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Supplementary materials 6-11
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Not applicable
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates
Reporting of discussion should include		
√	Quantitative assessment of bias	The systematic review is limited in scope, as it involves studies with limited information.

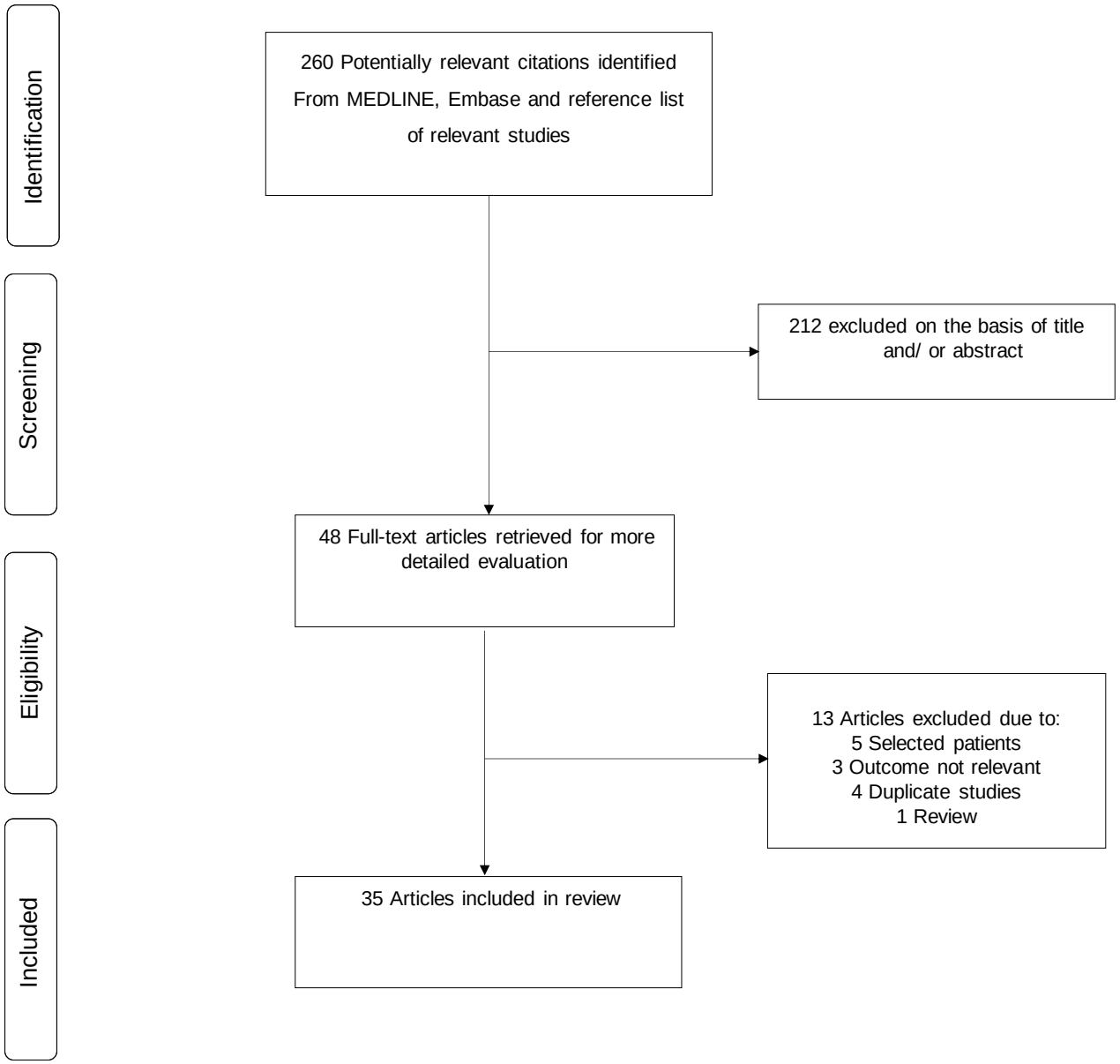
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in 'Methods' section
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Discussion
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	We recommend large-scale studies when more data becomes available
√	Disclosure of funding source	In "Funding" section

Supplementary Material 3: MEDLINE literature search strategy

1 exp Venous Thromboembolism/ (10672)
2 exp Thrombosis/ (129013)
3 exp Embolism/ (59862)
4 exp Pulmonary Embolism/ (38714)
5 exp Venous Thrombosis/ (54686)
6 exp Stroke/ (133752)
7 exp Acute Coronary Syndrome/ (15477)
8 exp Myocardial Infarction/ (174615)
9 exp Disseminated Intravascular Coagulation/ (10985)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (492282)
11 limit 10 to (english language and humans and yr="2020 -Current" and covid-19) (162)

Each part was specifically translated for searching alternative databases.

Supplementary Material 4: Selection of studies included in the meta-analysis



Supplementary Material 5: Reference list of included studies

[1] S. Aggarwal, N. Garcia-Telles, G. Aggarwal, C. Lavie, G. Lippi, B.M. Henry, Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States, Diagnosis (Berl) 7(2) (2020) 91-96.

[2] T. Chen, D. Wu, H. Chen, W. Yan, D. Yang, G. Chen, K. Ma, D. Xu, H. Yu, H. Wang, T. Wang, W. Guo, J. Chen, C. Ding, X. Zhang, J. Huang, M. Han, S. Li, X. Luo, J. Zhao, Q. Ning, Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study, BMJ 368 (2020) m1091.

[3] Y. Du, L. Tu, P. Zhu, M. Mu, R. Wang, P. Yang, X. Wang, C. Hu, R. Ping, P. Hu, T. Li, F. Cao, C. Chang, Q. Hu, Y. Jin, G. Xu, Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study, Am J Respir Crit Care Med (2020).

[4] M. Artifoni, G. Danic, G. Gautier, P. Gicquel, D. Boutoille, F. Raffi, A. Neel, R. Lecomte, Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors, J Thromb Thrombolysis 50(1) (2020) 211-216.

[5] S. Cui, S. Chen, X. Li, S. Liu, F. Wang, Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia, Journal of thrombosis and haemostasis : JTH 18(6) (2020) 1421-1424.

[6] P. Demelo-Rodriguez, E. Cervilla-Munoz, L. Ordieres-Ortega, A. Parra-Virto, M. Toledano-Macias, N. Toledo-Samaniego, A. Garcia-Garcia, I. Garcia-Fernandez-Bravo, Z. Ji, J. de-Miguel-Diez, L.A. Alvarez-Sala-Walther, J. Del-Toro-Cervera, F. Galeano-Valle, Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels, Thromb Res 192 (2020) 23-26.

[7] P. Faggiano, A. Bonelli, S. Paris, G. Milesi, S. Bisegna, N. Bernardi, A. Curnis, E. Agricola, R. Maroldi, Acute pulmonary embolism in COVID-19 disease: Preliminary report on seven patients, Int J Cardiol 313 (2020) 129-131.

[8] J. Helms, S. Kremer, H. Merdji, R. Clere-Jehl, M. Schenck, C. Kummerlen, O. Collange, C. Boulay, S. Fafi-Kremer, M. Ohana, M. Anheim, F. Meziani, Neurologic Features in Severe SARS-CoV-2 Infection, N Engl J Med 382(23) (2020) 2268-2270.

[9] F.A. Klok, M. Kruip, N.J.M. van der Meer, M.S. Arbous, D. Gommers, K.M. Kant, F.H.J. Kaptein, J. van Paassen, M.A.M. Stals, M.V. Huisman, H. Endeman, Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis, Thromb Res 191 (2020) 148-150.

[10] C. Lodigiani, G. Iapichino, L. Carenzo, M. Cecconi, P. Ferrazzi, T. Sebastian, N. Kucher, J.D. Studt, C. Sacco, B. Alexia, M.T. Sandri, S. Barco, C.-T.F. Humanitas, Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy, Thromb Res 191 (2020) 9-14.

[11] D. Mazzaccaro, F. Giacomazzi, M. Giannetta, A. Varriale, R. Scaramuzzo, A. Modafferi, G. Malacrida, P. Righini, M.M. Marrocco-Trischitta, G. Nano, Non-Overt Coagulopathy in Non-ICU Patients with Mild to Moderate COVID-19 Pneumonia, J Clin Med 9(6) (2020).

[12] W. Thomas, J. Varley, A. Johnston, E. Symington, M. Robinson, K. Sheares, A. Lavinio, M. Besser, Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom, Thromb Res 191 (2020) 76-77.

[13] J. Poissy, J. Goutay, M. Caplan, E. Parmentier, T. Duburcq, F. Lassalle, E. Jeanpierre, A. Rauch, J. Labreuche, S. Susen, I.C.U.H.C.-g. Lille, Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence, Circulation (2020).

[14] S. Middeldorp, M. Coppens, T.F. van Haaps, M. Foppen, A.P. Vlaar, M.C.A. Muller, C.C.S. Bouman, L.F.M. Beenen, R.S. Kootte, J. Heijmans, L.P. Smits, P.I. Bonta, N. van Es, Incidence of venous

thromboembolism in hospitalized patients with COVID-19, Journal of thrombosis and haemostasis : JTH (2020).

[15] L. Mao, H. Jin, M. Wang, Y. Hu, S. Chen, Q. He, J. Chang, C. Hong, Y. Zhou, D. Wang, X. Miao, Y. Li, B. Hu, Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China, JAMA Neurol (2020).

[16] J.F. Llitjos, M. Leclerc, C. Chochois, J.M. Monsallier, M. Ramakers, M. Auvray, K. Merouani, High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients, Journal of thrombosis and haemostasis : JTH (2020).

[17] I. Leonard-Lorant, X. Delabranche, F. Severac, J. Helms, C. Pauzet, O. Collange, F. Schneider, A. Labani, P. Bilbault, S. Moliere, P. Leyendecker, C. Roy, M. Ohana, Acute Pulmonary Embolism in COVID-19 Patients on CT Angiography and Relationship to D-Dimer Levels, Radiology (2020) 201561.

[18] F. Grillet, J. Behr, P. Calame, S. Aubry, E. Delabrousse, Acute Pulmonary Embolism Associated with COVID-19 Pneumonia Detected by Pulmonary CT Angiography, Radiology (2020) 201544.

[19] A. Longchamp, J. Longchamp, S. Manzocchi-Besson, L. Whiting, C. Haller, S. Jeanneret, M. Godio, J.J. Garcia Martinez, T. Bonjour, M. Caillat, G. Maitre, J.M. Thaler, R. Pantet, V. Donner, A. Dumoulin, S. Emonet, G. Greub, R. Friolet, H. Robert-Ebadi, M. Righini, B. Sanchez, J. Delaloye, Venous Thromboembolism in Critically Ill Patients with Covid-19: Results of a Screening Study for Deep Vein Thrombosis, Research and Practice in Thrombosis and Haemostasis n/a(n/a) (2020).

[20] M. Moll, R.L. Zon, K.W. Sylvester, E.C. Chen, V. Cheng, N.T. Connell, L.E. Fredenburgh, R.M. Baron, M.H. Cho, A.E. Woolley, J.M. Connors, Venous Thromboembolism in COVID-19 ICU Patients, Chest (2020).

[21] C. Fang, G. Garzillo, B. Batohi, J.T.H. Teo, M. Berovic, P.S. Sidhu, H. Robbie, Extent of pulmonary thromboembolic disease in patients with COVID-19 on CT: relationship with pulmonary parenchymal disease, Clin Radiol (2020).

[22] F. Mei, J. Fan, J. Yuan, Z. Liang, K. Wang, J. Sun, W. Guan, M. Huang, Y. Li, W.W. Zhang, Comparison of Venous Thromboembolism Risks Between COVID-19 Pneumonia and Community-Acquired Pneumonia Patients, Arterioscler Thromb Vasc Biol (2020) ATVBAHA120314779.

[23] Y. Li, M. Li, M. Wang, Y. Zhou, J. Chang, Y. Xian, D. Wang, L. Mao, H. Jin, B. Hu, Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study, Stroke Vasc Neurol (2020).

[24] S.M. Stoneham, K.M. Milne, E. Nuttall, G.H. Frew, B.R. Sturrock, H. Sivaloganathan, E.E. Ladikou, S. Drage, B. Phillips, T.J. Chevassut, A.C. Eziefula, Thrombotic risk in COVID-19: a case series and case-control study, Clin Med (Lond) 20(4) (2020) e76-e81.

[25] R.M. Inciardi, M. Adamo, L. Lupi, D.S. Cani, M. Di Pasquale, D. Tomasoni, L. Italia, G. Zaccone, C. Tedino, D. Fabbricatore, A. Curnis, P. Faggiano, E. Gorga, C.M. Lombardi, G. Milesi, E. Vizzardi, M. Volpini, S. Nodari, C. Specchia, R. Maroldi, M. Bezzi, M. Metra, Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy, Eur Heart J 41(19) (2020) 1821-1829.

[26] S. Bilaloglu, Y. Aphinyanaphongs, S. Jones, E. Iturrate, J. Hochman, J.S. Berger, Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System, JAMA (2020).

[27] A.E. Merkler, N.S. Parikh, S. Mir, A. Gupta, H. Kamel, E. Lin, J. Lantos, E.J. Schenck, P. Goyal, S.S. Bruce, J. Kahan, K.N. Lansdale, N.M. LeMoss, S.B. Murthy, P.E. Stieg, M.E. Fink, C. Iadecola, A.Z. Segal, M. Cusick, T.R. Campion, Jr., I. Diaz, C. Zhang, B.B. Navi, Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza, JAMA Neurol (2020).

[28] B. Ren, F. Yan, Z. Deng, S. Zhang, L. Xiao, M. Wu, L. Cai, Extremely High Incidence of Lower Extremity Deep Venous Thrombosis in 48 Patients With Severe COVID-19 in Wuhan, Circulation 142(2) (2020) 181-183.

[29] M. Rieder, I. Goller, M. Jeserich, N. Baldus, L. Pollmeier, L. Wirth, A. Supady, C. Bode, H.J. Busch, B. Schmid, D. Duerschmied, N. Gauchel, A. Lother, Rate of venous thromboembolism in a prospective all-comers cohort with COVID-19, J Thromb Thrombolysis (2020).

[30] A. Santoliquido, A. Porfidia, A. Nesci, G. De Matteis, G. Marrone, E. Porceddu, G. Camma, I. Giarretta, M. Fantoni, F. Landi, A. Gasbarrini, R. Pola, G.A.C.-. Group, Incidence of Deep Vein Thrombosis among non-ICU Patients Hospitalized for COVID-19 Despite Pharmacological Thromboprophylaxis, Journal of thrombosis and haemostasis : JTH (2020).

[31] G. Tavazzi, L. Civardi, L. Caneva, S. Mongodi, F. Mojoli, Thrombotic events in SARS-CoV-2 patients: an urgent call for ultrasound screening, Intensive Care Med 46(6) (2020) 1121-1123.

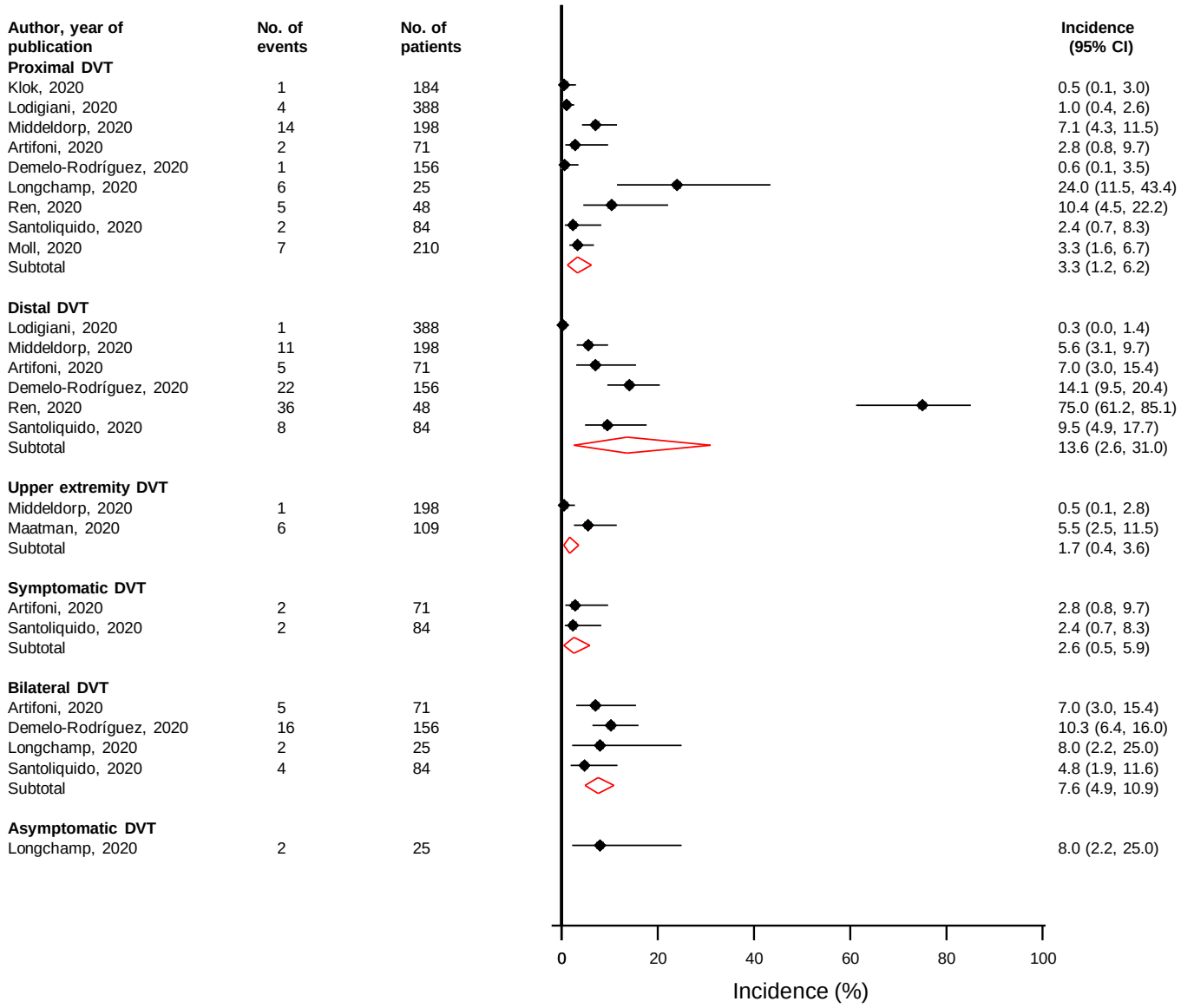
[32] R.A. Trigonis, D.B. Holt, R. Yuan, A.A. Siddiqui, M.K. Craft, B.A. Khan, R. Kapoor, O. Rahman, Incidence of Venous Thromboembolism in Critically Ill Coronavirus Disease 2019 Patients Receiving Prophylactic Anticoagulation, Crit Care Med (2020).

[33] M. Fraisse, E. Logre, O. Pajot, H. Mentec, G. Plantefeve, D. Contou, Thrombotic and hemorrhagic events in critically ill COVID-19 patients: a French monocenter retrospective study, Crit Care 24(1) (2020) 275.

[34] M.J.R. Desborough, A.J. Doyle, A. Griffiths, A. Retter, K.A. Breen, B.J. Hunt, Image-proven thromboembolism in patients with severe COVID-19 in a tertiary critical care unit in the United Kingdom, Thromb Res 193 (2020) 1-4.

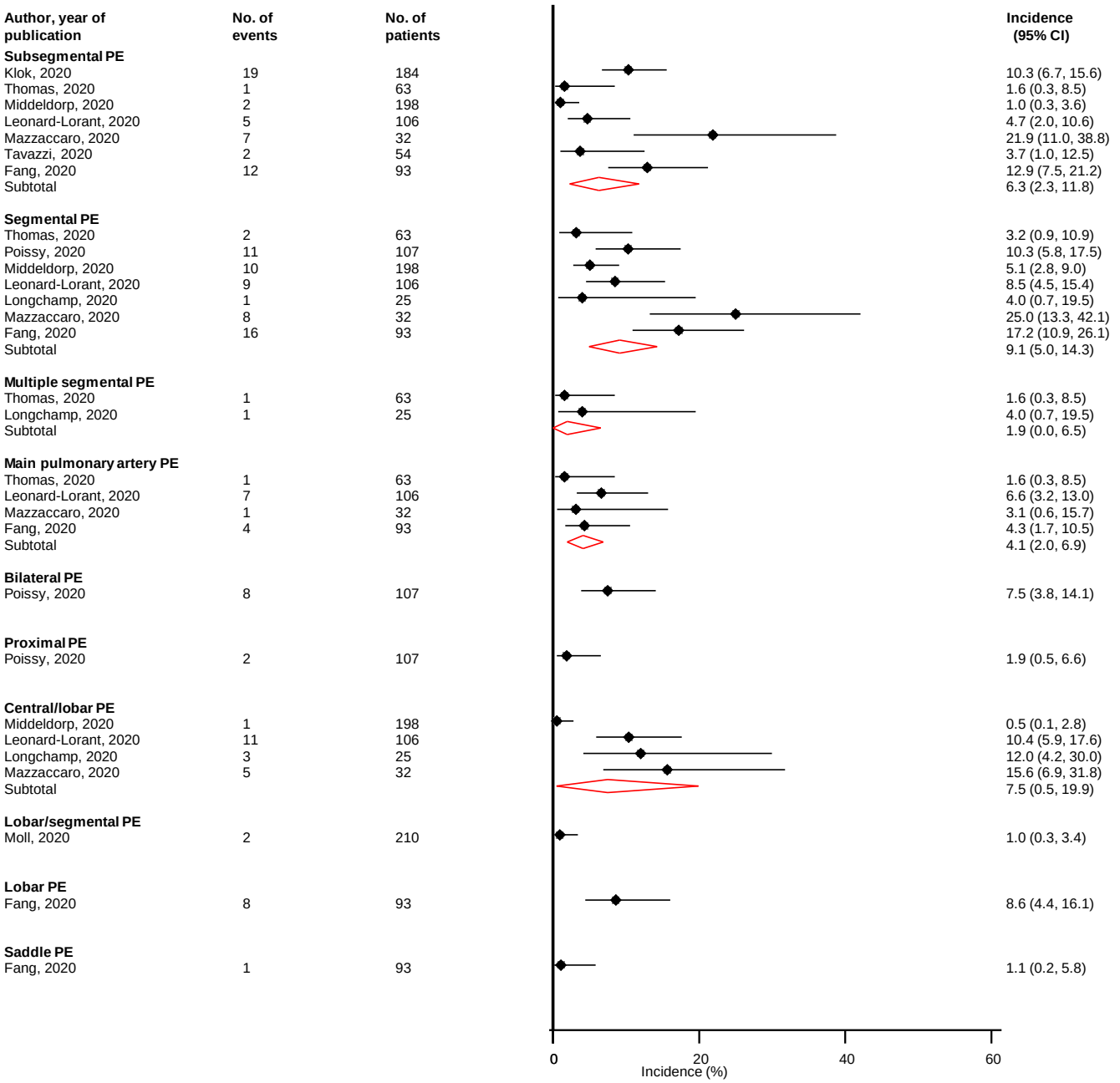
[35] T.K. Maatman, F. Jalali, C. Feizpour, A. Douglas, 2nd, S.P. McGuire, G. Kinnaman, J.L. Hartwell, B.T. Maatman, R.P. Kreutz, R. Kapoor, O. Rahman, N.J. Zyromski, A.D. Meagher, Routine Venous Thromboembolism Prophylaxis May Be Inadequate in the Hypercoagulable State of Severe Coronavirus Disease 2019, Crit Care Med (2020).

Supplementary Material 6: Incidence of deep vein thrombosis subtypes in COVID-19 patients



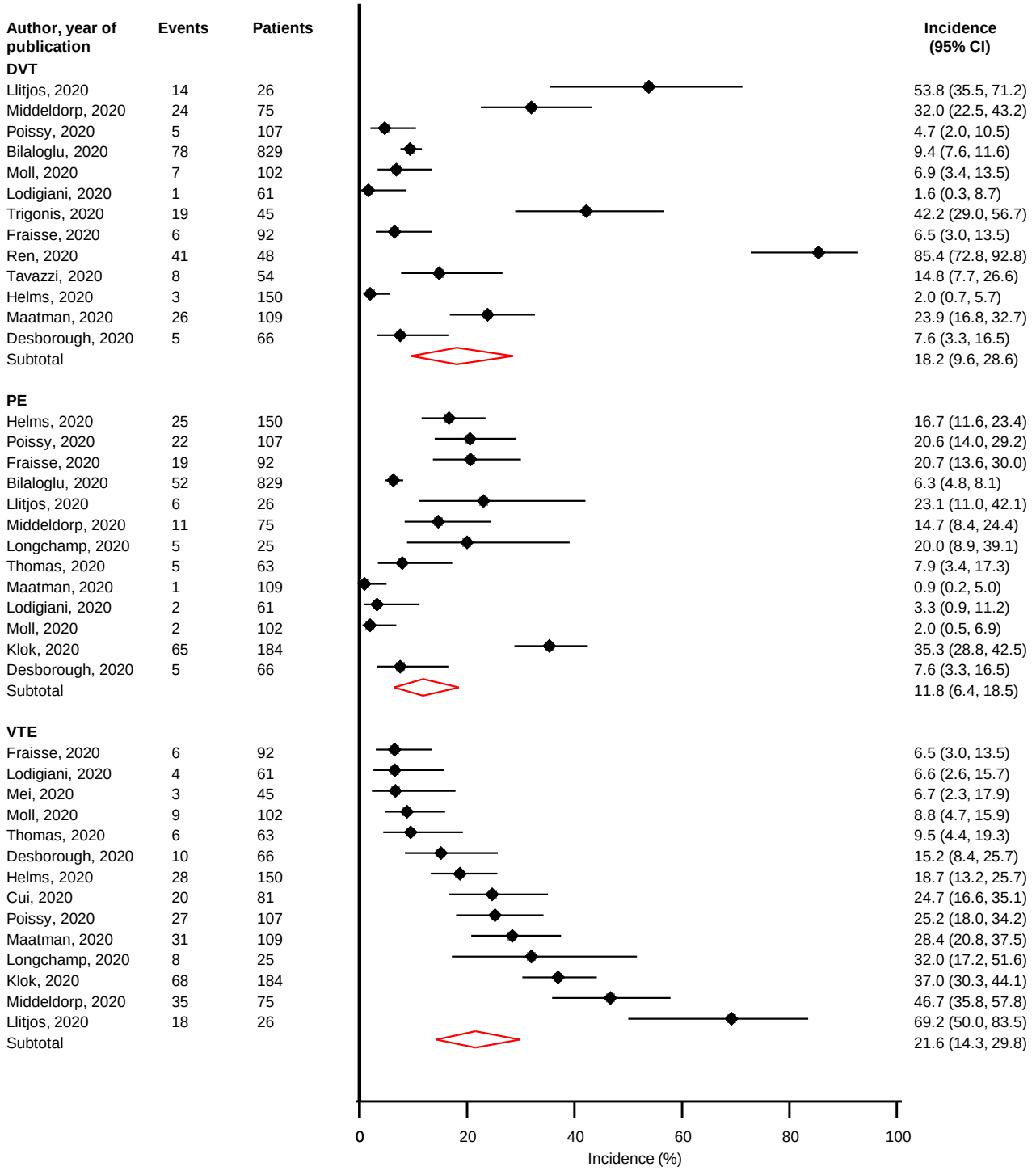
CI, confidence interval (bars); DVT, deep vein thrombosis

Supplementary Material 7: Incidence of pulmonary embolism subtypes in COVID-19 patients



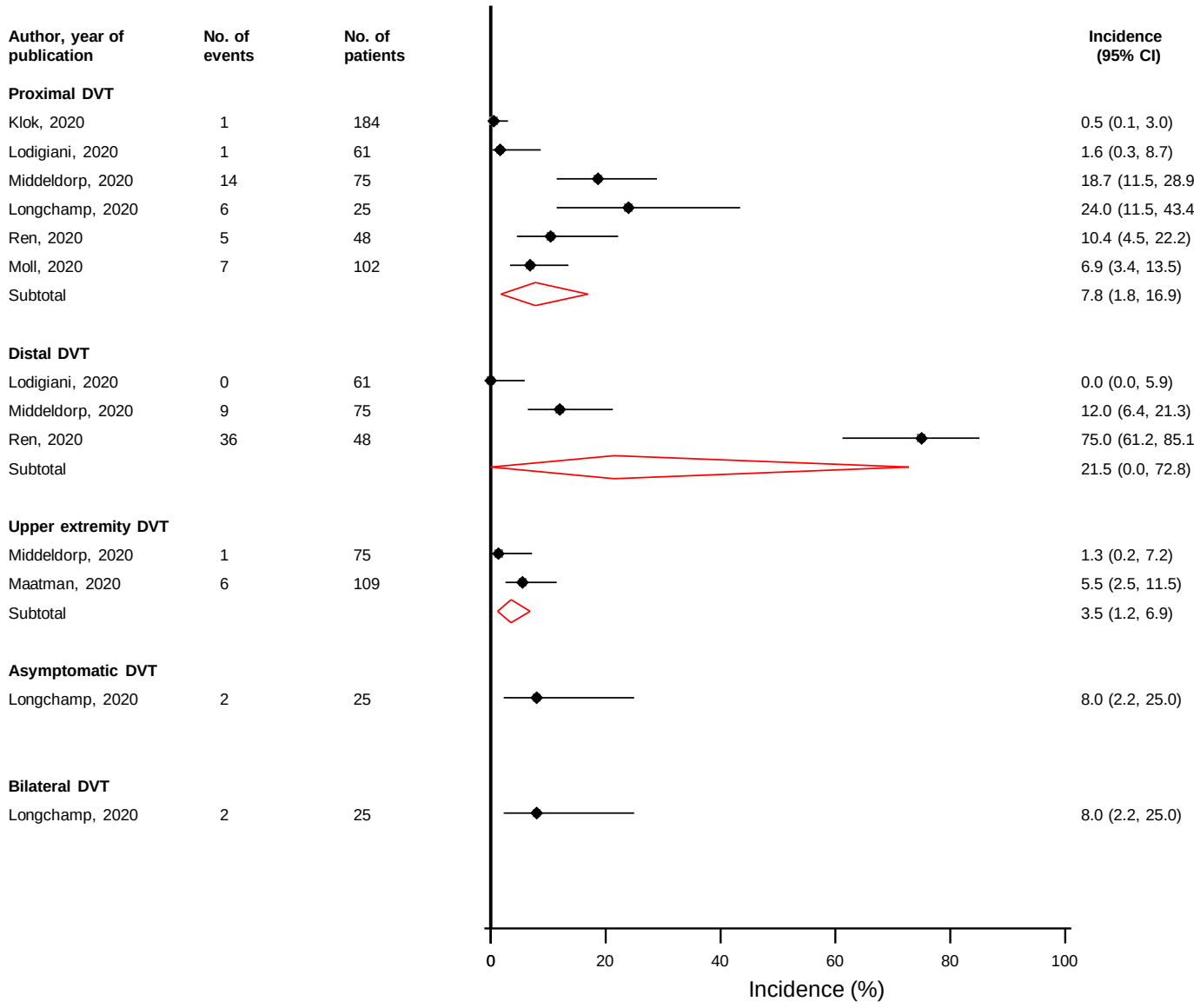
CI, confidence interval (bars); PE, pulmonary embolism

Supplementary Material 8: Incidence of venous thromboembolic complications in severe COVID-19 patients



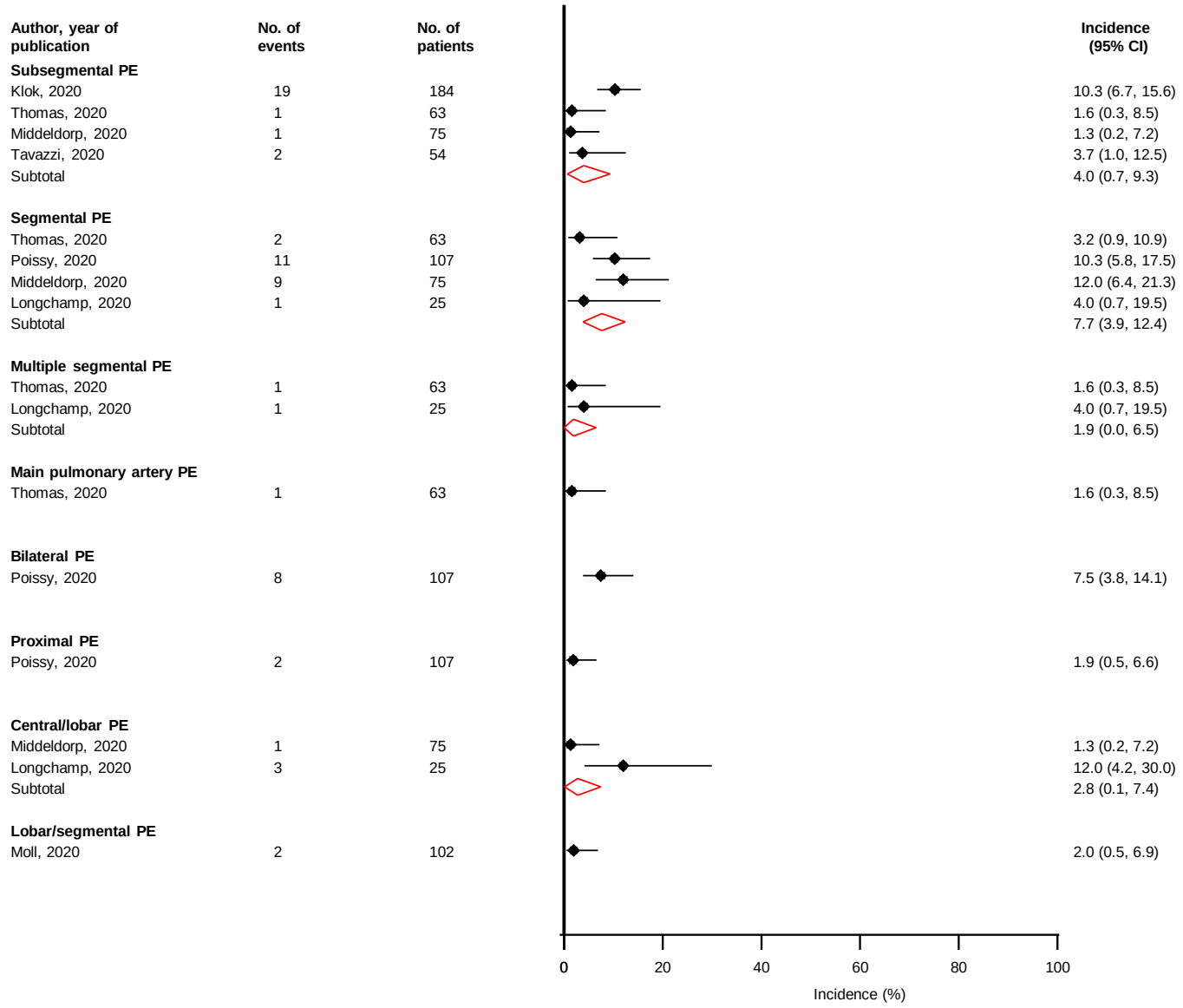
CI, confidence interval (bars); DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

Supplementary Material 9: Incidence of deep vein thrombosis subtypes in severe COVID-19 patients



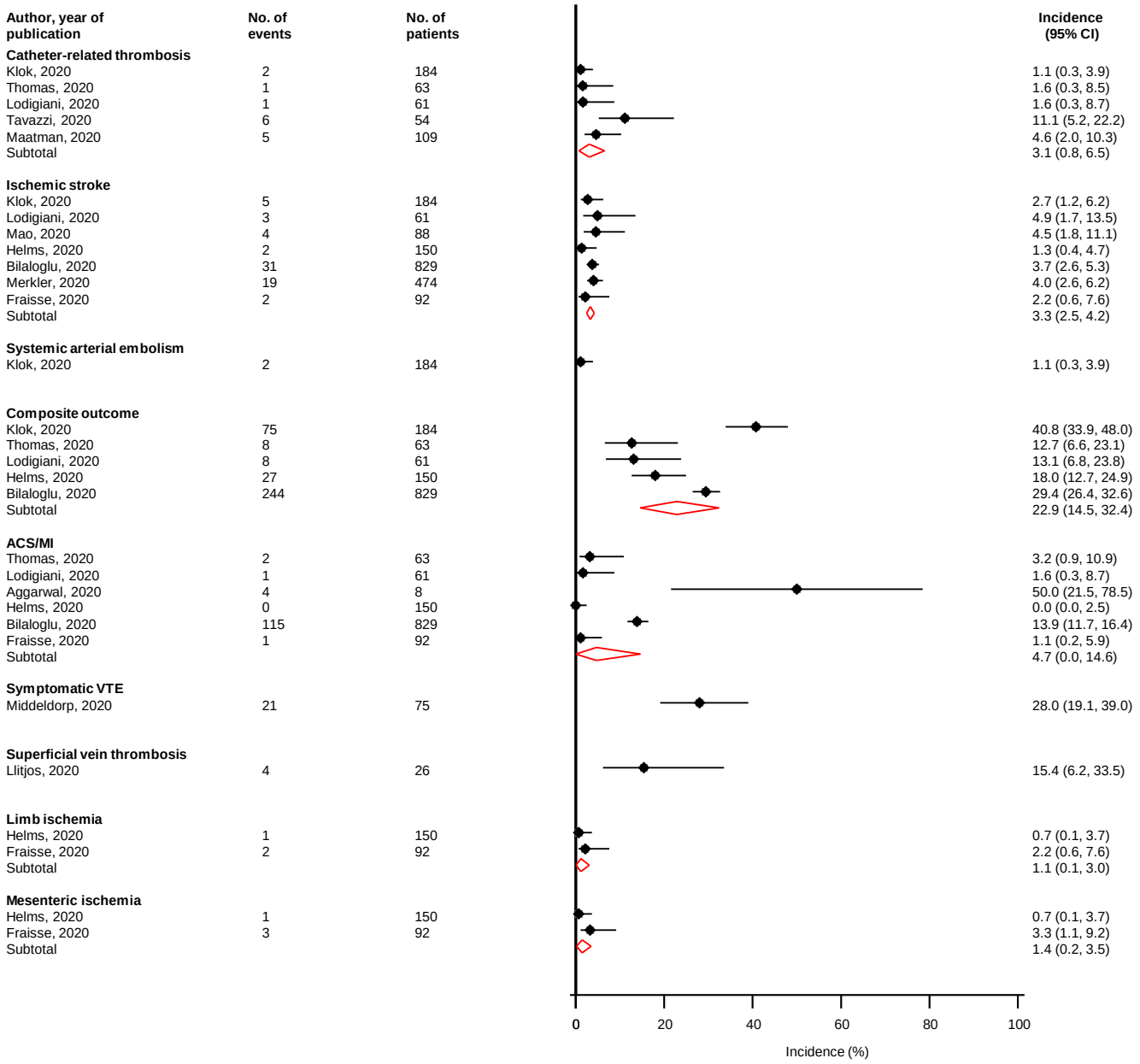
CI, confidence interval (bars); DVT, deep vein thrombosis

Supplementary Material 10: Incidence of pulmonary embolism subtypes in severe COVID-19 patients



CI, confidence interval (bars); PE, pulmonary embolism

Supplementary Material 11: Incidence of other venous and arterial thromboembolic complications in severe COVID-19 patients



ACS, acute coronary syndrome; CI, confidence interval (bars); MI, myocardial infarction; VTE, venous thromboembolism

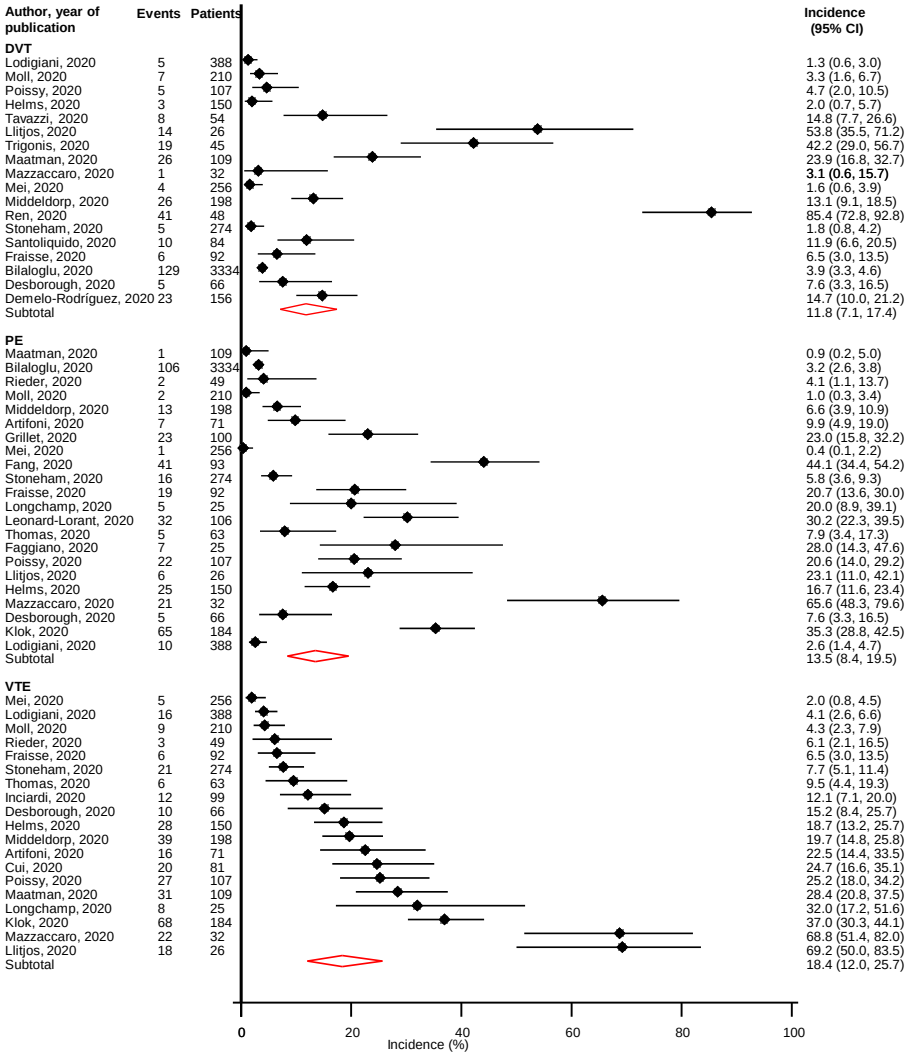
Composite outcome refers to the composite outcome of arterial and venous thromboembolic disease

Table 1. Baseline characteristics of 35 eligible studies

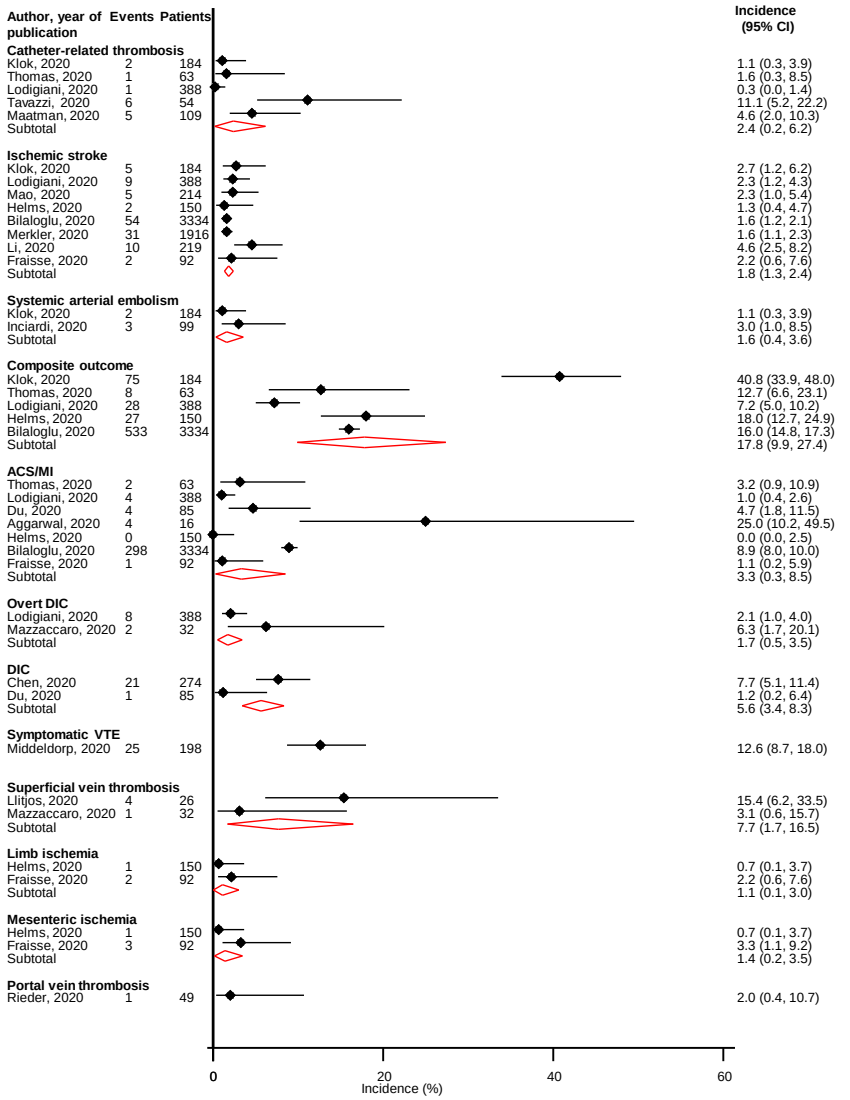
Author, year of publication	Source of patients	Country	Date of data collection	Mean/median age (years)	% males	No. of patients	NOS
Klok, 2020	Dutch Univesity Hospitals	Netherlands	March - April 2020	64.0	76	184	6
Thomas, 2020	Adenbrooke's Hospital	UK	Up to April 2020	20-89*	69	63	4
Lodigiani, 2020	University Hospital, Milan	Italy	Feb - April 2020	66.0	68	388	4
Cui, 2020	Union Hospital, Wuhan	China	Jan - March 2020	59.9	46	81	4
Chen, 2020	Tongji Hospital in Wuhan	China	Jan - Feb 2020	62.0	62	274	4
Du, 2020	Hannan Hospital and Wuhan Union Hospital	China	Jan - Feb 2020	65.8	72.9	85	4
Aggarwal, 2020	UnityPoint Clinic	USA	March - April 2020	67.0	75	16	4
Poissy, 2020	Lille Hospital	France	Feb - March 2020	NR	NR	107	4
Middeldorp, 2020	Amsterdam Academic Medical Center	Netherlands	March - April 2020	61.0	66	198	6
Mao, 2020	Union Hospital of Huazhong University of Science and Technology	China	Jan - Feb 2020	52.7	40.7	214	4
Llitjos, 2020	2 French ICUs	France	March - April 2020	68.0	77	26	4
Leonard-Lorant, 2020	Strasbourg University Hospital	France	March, 2020	64.0	66	106	4
Helms, 2020	French Tertiary Hospital	France	March 2020	63.0	81.3	150	4
Grillet, 2020	Centre Hospitalier Universitaire de Besancon	France	March – April 2020	66.0	70	100	4
Artifoni, 2020	Nantes University Hospital and Châteaubriant Hospital	France	March - April 2020	64.0	60.6	71	4
Demelo-Rodríguez, 2020	Third-level hospital in Madrid	Spain	April, 2020	68.1	65.4	156	5
Faggiano, 2020	NR	Italy	NR	71.0	84	25	4
Longchamp, 2020	Sion hospital ICU	Switzerland	March - April 2020	68.0	64	25	4
Mazzaccaro, 2020	IRCCS Ospedale San Raaele	Italy	March - April 2020	68.6	71.9	32	4
Bilaloglu, 2020	NYU Langone Health	USA	March - April 2020	64.0	60.4	3,334	6
Merkler, 2020	Academic Hospitals in New York	USA	March - May 2020	64.0	57.5	1,916	6
Ren, 2020	Zhongnan and Leishenshan Hospitals	China	Feb - March 2020	70.0	54.2	48	4
Rieder, 2020	University Medical Center—University of Freiburg	Germany	March - April 2020	60.0	61.2	49	4
Santoliquido, 2020	Fondazione Policlinico Universitario A. Gemelli IRCCS	Italy	April, 2020	67.6	72.6	84	4
Tavazzi, 2020	ICU of a Hub Hospital	Italy	Up to Feb 2020	68.0	83.0	54	4
Trigonis, 2020	IU Health Methodist Hospital	USA	March - April 2020	60.8	NR	45	4
Moll, 2020	Brigham and Women’s Hospital	USA	March - April 2020	62.2	48.1	210	4
Fang, 2020	King’s College Hospital NHS Foundation Trust	UK	March - April 2020	59.2	64.5	93	4
Mei, 2020	Yichang Central People's Hospital	China	Jan - March 2020	55.5	51.2	256	4
Li, 2020	Union Hospital of Huazhong University of Science and Technology	China	Jan - March 2020	53.3	40.6	219	4
Stoneham, 2020	Brighton and Sussex University Hospitals NHS Trust	UK	March - April 2020	NR	NR	274	5
Inciardi, 2020	Civil Hospitals of Brescia	Italy	March, 2020	67.0	81.0	99	4
Fraisse, 2020	Centre Hospitalier Victor Dupouy	France	March - April 2020	61.0	79.0	92	4
Desborough, 2020	Guy's and St Thomas' NHS Foundation Trust	UK	March, 2020	59.0	73.0	66	4
Maatman, 2020	Indianapolis area academic hospitals	USA	March - May 2020	61.0	57.0	109	4

ICU, intensive care unit; NOS, Newcastle Ottawa Scale; NR, not reported; *, age range

A.


Author, year of publication
Events
Patients
Incidence (95% CI)
DVT
Lodigiani, 2020 5 388 1.3 (0.6, 3.0)
Moll, 2020 7 210 3.3 (1.6, 6.7)
Poissy, 2020 5 107 4.7 (2.0, 10.5)
Helms, 2020 3 150 2.0 (0.7, 5.7)
Tavazzi, 2020 8 54 14.8 (7.7, 26.6)
Llitjos, 2020 14 26 53.8 (35.5, 71.2)
Trigonis, 2020 19 45 42.2 (29.0, 56.7)
Maatman, 2020 26 109 23.9 (16.8, 32.7)
Mazzaccaro, 2020 1 32 3.1 (0.6, 15.7)
Mei, 2020 4 256 1.6 (0.6, 3.9)
Middeldorp, 2020 26 198 13.1 (9.1, 18.5)
Ren, 2020 41 48 85.4 (72.8, 92.8)
Stoneham, 2020 5 274 1.8 (0.8, 4.2)
Santoliquido, 2020 10 84 11.9 (6.6, 20.5)
Fraisse, 2020 6 92 6.5 (3.0, 13.5)
Bilaloglu, 2020 129 3334 3.9 (3.3, 4.6)
Desborough, 2020 5 66 7.6 (3.3, 16.5)
Demelo-Rodríguez, 2020 23 156 14.7 (10.0, 21.2)
Subtotal 11.8 (7.1, 17.4)
PE
Maatman, 2020 1 109 0.9 (0.2, 5.0)
Bilaloglu, 2020 106 3334 3.2 (2.6, 3.8)
Rieder, 2020 2 49 4.1 (1.1, 13.7)
Moll, 2020 2 210 1.0 (0.3, 3.4)
Middeldorp, 2020 13 198 6.6 (3.9, 10.9)
Artifoni, 2020 7 71 9.9 (4.9, 19.0)
Grillet, 2020 23 100 23.0 (15.8, 32.2)
Mei, 2020 1 256 0.4 (0.1, 2.2)
Fang, 2020 41 93 44.1 (34.4, 54.2)
Stoneham, 2020 16 274 5.8 (3.6, 9.3)
Fraisse, 2020 19 92 20.7 (13.6, 30.0)
Longchamp, 2020 5 25 20.0 (8.9, 39.1)
Leonard-Lorant, 2020 32 106 30.2 (22.3, 39.5)
Thomas, 2020 5 63 7.9 (3.4, 17.3)
Faggiano, 2020 7 25 28.0 (14.3, 47.6)
Poissy, 2020 22 107 20.6 (14.0, 29.2)
Llitjos, 2020 6 26 23.1 (11.0, 42.1)
Helms, 2020 25 150 16.7 (11.6, 23.4)
Mazzaccaro, 2020 21 32 65.6 (48.3, 79.6)
Desborough, 2020 5 66 7.6 (3.3, 16.5)
Klok, 2020 65 184 35.3 (28.8, 42.5)
Lodigiani, 2020 10 388 2.6 (1.4, 4.7)
Subtotal 13.5 (8.4, 19.5)
VTE
Mei, 2020 5 256 2.0 (0.8, 4.5)
Lodigiani, 2020 16 388 4.1 (2.6, 6.6)
Moll, 2020 9 210 4.3 (2.3, 7.9)
Rieder, 2020 3 49 6.1 (2.1, 16.5)
Fraisse, 2020 6 92 6.5 (3.0, 13.5)
Stoneham, 2020 21 274 7.7 (5.1, 11.4)
Thomas, 2020 6 63 9.5 (4.4, 19.3)
Inciardi, 2020 12 99 12.1 (7.1, 20.0)
Desborough, 2020 10 66 15.2 (8.4, 25.7)
Helms, 2020 28 150 18.7 (13.2, 25.7)
Middeldorp, 2020 39 198 19.7 (14.8, 25.8)
Artifoni, 2020 16 71 22.5 (14.4, 33.5)
Cui, 2020 20 81 24.7 (16.6, 35.1)
Poissy, 2020 27 107 25.2 (18.0, 34.2)
Maatman, 2020 31 109 28.4 (20.8, 37.5)
Longchamp, 2020 8 25 32.0 (17.2, 51.6)
Klok, 2020 68 184 37.0 (30.3, 44.1)
Mazzaccaro, 2020 22 32 68.8 (51.4, 82.0)
Llitjos, 2020 18 26 69.2 (50.0, 83.5)
Subtotal 18.4 (12.0, 25.7)
0
20
40
60
80
100
Incidence (%)

B.


Author, year of publication
Events
Patients
Incidence (95% CI)
Catheter-related thrombosis
Klok, 2020 2 184 1.1 (0.3, 3.9)
Thomas, 2020 1 63 1.6 (0.3, 8.5)
Lodigiani, 2020 1 388 0.3 (0.0, 1.4)
Tavazzi, 2020 6 54 11.1 (5.2, 22.2)
Maatman, 2020 5 109 4.6 (2.0, 10.3)
Subtotal 2.4 (0.2, 6.2)
Ischemic stroke
Klok, 2020 5 184 2.7 (1.2, 6.2)
Lodigiani, 2020 9 388 2.3 (1.2, 4.3)
Mao, 2020 5 214 2.3 (1.0, 5.4)
Helms, 2020 2 150 1.3 (0.4, 4.7)
Bilaloglu, 2020 54 3334 1.6 (1.2, 2.1)
Merkler, 2020 31 1916 1.6 (1.1, 2.3)
Li, 2020 10 219 4.6 (2.5, 8.2)
Fraisse, 2020 2 92 2.2 (0.6, 7.6)
Subtotal 1.8 (1.3, 2.4)
Systemic arterial embolism
Klok, 2020 2 184 1.1 (0.3, 3.9)
Inciardi, 2020 3 99 3.0 (1.0, 8.5)
Subtotal 1.6 (0.4, 3.6)
Composite outcome
Klok, 2020 75 184 40.8 (33.9, 48.0)
Thomas, 2020 8 63 12.7 (6.6, 23.1)
Lodigiani, 2020 28 388 7.2 (5.0, 10.2)
Helms, 2020 27 150 18.0 (12.7, 24.9)
Bilaloglu, 2020 533 3334 16.0 (14.8, 17.3)
Subtotal 17.8 (9.9, 27.4)
ACS/MI
Thomas, 2020 2 63 3.2 (0.9, 10.9)
Lodigiani, 2020 4 388 1.0 (0.4, 2.6)
Du, 2020 4 85 4.7 (1.8, 11.5)
Aggarwal, 2020 4 16 25.0 (10.2, 49.5)
Helms, 2020 0 150 0.0 (0.0, 2.5)
Bilaloglu, 2020 298 3334 8.9 (8.0, 10.0)
Fraisse, 2020 1 92 1.1 (0.2, 5.9)
Subtotal 3.3 (0.3, 8.5)
Overt DIC
Lodigiani, 2020 8 388 2.1 (1.0, 4.0)
Mazzaccaro, 2020 2 32 6.3 (1.7, 20.1)
Subtotal 1.7 (0.5, 3.5)
DIC
Chen, 2020 21 274 7.7 (5.1, 11.4)
Du, 2020 1 85 1.2 (0.2, 6.4)
Subtotal 5.6 (3.4, 8.3)
Symptomatic VTE
Middeldorp, 2020 25 198 12.6 (8.7, 18.0)
Superficial vein thrombosis
Llitjos, 2020 4 26 15.4 (6.2, 33.5)
Mazzaccaro, 2020 1 32 3.1 (0.6, 15.7)
Subtotal 7.7 (1.7, 16.5)
Limb ischemia
Helms, 2020 1 150 0.7 (0.1, 3.7)
Fraisse, 2020 2 92 2.2 (0.6, 7.6)
Subtotal 1.1 (0.1, 3.0)
Mesenteric ischemia
Helms, 2020 1 150 0.7 (0.1, 3.7)
Fraisse, 2020 3 92 3.3 (1.1, 9.2)
Subtotal 1.4 (0.2, 3.5)
Portal vein thrombosis
Rieder, 2020 1 49 2.0 (0.4, 10.7)
0
20
40
60
Incidence (%)