











METHODOLOGICAL ARTICLE

Estimating incidence of venous thromboembolism in COVID-19: Methodological considerations

Linda Nab MSc¹   | Rolf H. H. Groenwold MD, PhD^{1,2}   |
 Frederikus A. Klok MD, PhD³   | Soerajja Bhoelan MD⁴  |
 Marieke J. H. A. Kruij MD, PhD⁵  | Suzanne C. Cannegieter MD, PhD^{1,3}  

¹Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

²Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands

³Department of Medicine – Thrombosis and Haemostasis, Leiden University Medical Center, Leiden, The Netherlands

⁴Department of Haematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

⁵Department of Haematology, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence

Suzanne C. Cannegieter, Department of Clinical Epidemiology & Department of Thrombosis and Haemostasis, Leiden University Medical Center, Postzone C7-P, P.O. Box 9600, 2300 RC Leiden, The Netherlands.

Email: s.c.cannegieter@lumc.nl

Funding information

Netherlands Organization for Health Research and Development, Grant/Award Number: 10430012010004; Trombosetichting Nederland, Grant/Award Number: 2020_A

Handling Editor: Dr Lana Castellucci

Abstract

Background: Coagulation abnormalities and coagulopathy are recognized as consequences of severe acute respiratory syndrome coronavirus 2 infection and the resulting coronavirus disease 2019 (COVID-19). Specifically, venous thromboembolism (VTE) has been reported as a frequent complication. By May 27, 2021, at least 93 original studies and 25 meta-analyses investigating VTE incidence in patients with COVID-19 had been published, showing large heterogeneity in reported VTE incidence ranging from 0% to 85%. This large variation complicates interpretation of individual study results as well as comparisons across studies, for example, to investigate changes in incidence over time, compare subgroups, and perform meta-analyses.

Objectives: This study sets out to provide an overview of sources of heterogeneity in VTE incidence studies in patients with COVID-19, illustrated using examples.

Methods: The original studies of three meta-analyses were screened and a list of sources of heterogeneity that may explain observed heterogeneity across studies was composed.

Results: The sources of heterogeneity in VTE incidence were classified as clinical sources and methodologic sources. Clinical sources of heterogeneity include differences between studies regarding patient characteristics that affect baseline VTE risk and protocols used for VTE testing. Methodologic sources of heterogeneity include differences in VTE inclusion types, data quality, and the methods used for data analysis.

Conclusions: To appreciate reported estimates of VTE incidence in patients with COVID-19 in relation to its etiology, prevention, and treatment, researchers should unambiguously report about possible clinical and methodological sources of heterogeneity in those estimates. This article provides suggestions for that.

KEYWORDS

COVID-19, incidence, meta-analysis, SARS-CoV-2, venous thromboembolism

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Research and Practice in Thrombosis and Haemostasis* published by Wiley Periodicals LLC on behalf of International Society on Thrombosis and Haemostasis (ISTH).

Essentials

- Incidence studies of venous thromboembolism in patients with COVID-19 show large heterogeneity.
- Clinical sources and methodological sources of heterogeneity were identified and illustrated with examples.
- The classification of these sources of heterogeneity informed suggestions for improved reporting.
- Description of these elements may better isolate important differences in reports of incidences.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily affects the respiratory system, but coagulation abnormalities and coagulopathy are also recognized as consequences.¹ In particular, venous thromboembolism (VTE) has been reported as a major complication, with VTE incidences up to 50% in intensive care unit (ICU)-admitted patients.² By May 27, 2021, already 25 systematic reviews investigating VTE incidence in patients with COVID-19 had been published,³⁻²⁷ of which the most recent meta-analysis by Kollias et al.⁵ identified 93 unique studies on VTE incidence.

Systematic reviews of VTE incidence in patients with COVID-19 show large heterogeneity.^{5,12,27} For instance, Nopp et al.¹² described VTE incidences in hospital-admitted patients ranging from 0% to 40.3%, while Jiménez et al.²⁷ reported VTE incidences between 0% and 85%. Kollias et al. restricted their systematic review to studies that performed “screening/assessment in the total sample for DVT (lower limb ultrasonography) or were focused on patients with suspicion for PE (whole study population subjected to tomography pulmonary angiogram),” but despite this restriction, they found heterogenous VTE incidences ranging between 0% and 85%.⁵ Possible explanations for this heterogeneity in VTE incidence include differences in design of the study, clinical setting, and local practice (e.g., thromboprophylaxis strategy),¹² differences in end point definition, testing strategies, and patients' characteristics.²⁷

The wide variation in VTE incidence not only raises questions about the interpretation of individual study results but, more importantly, complicates comparisons between studies to investigate, for example, changes over time, in subgroups, and to perform meta-analyses. To appreciate reported VTE incidences and to diminish their heterogeneity, it is important to understand different sources of this heterogeneity across studies. Therefore, we provide an overview of such sources of heterogeneity in VTE incidence studies on COVID-19 and illustrate this using various examples. Conclusively, we add a list of essential information to report to improve consistency and hence the relevance of studies on VTE incidence in patients with COVID-19.

2 | METHODS

The large heterogeneity in VTE incidence across studies found in the meta-analyses by Jiménez et al.²⁷ and Nopp et al.¹² incentivized this project. On May 27, 2021, a pragmatic search on PubMed using

the search string “meta-analysis covid-19 venous thromboembolism” was performed resulting in a rough estimate of the number of meta-analyses published. Twenty-five meta-analyses were identified. The most recent meta-analysis was published on April 4, 2021, by Kollias et al.⁵ The individual VTE incidence studies included in the meta-analyses by Jiménez et al., Nopp et al., and Kollias et al. were screened, and an initial list of potential sources of heterogeneity was created through discussions by authors LN, RHHG, and SCC. The initial list was discussed in meetings with authors FAK, BSB, and MJHAK and revised until consensus was reached. For educational purposes, an example was sought for each listed source of heterogeneity by identifying two heterogenous studies also showing heterogeneity in their estimated VTE incidence, without taking other explanations into account. For consistency, incidences of all VTE incidence studies reported in this study were calculated as “number of cases during the entire study follow up divided by the size of the study population” and accompanied by a 95% Wald-based confidence interval (CI).

3 | SOURCES OF HETEROGENEITY OF VTE INCIDENCE STUDIES

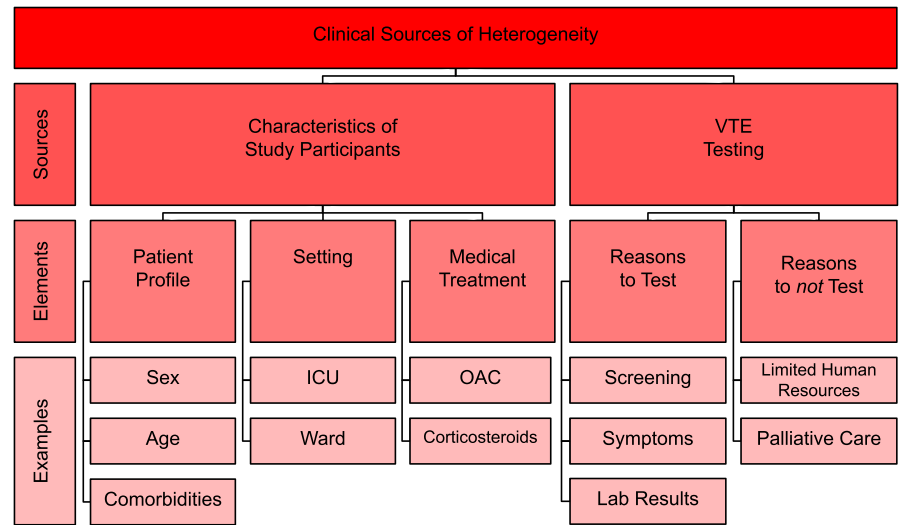
Figures 1 and 2 provide an overview of the identified sources of variation in VTE incidence studies. A distinction was made between clinical (Figure 1) and methodologic sources (Figure 2). Clinical sources of heterogeneity include differences related to study characteristics affecting VTE risk and VTE testing. Methodologic sources of heterogeneity refer to differences in VTE manifestation inclusion types (e.g., inclusion of deep vein thrombosis [DVT], pulmonary embolism [PE] or both), data quality, and the analytical methods used, that is, what method was used to estimate VTE incidence and how limitations of the data were handled. These clinical and methodologic sources are explained in more detail below.

3.1 | Clinical sources of heterogeneity

3.1.1 | Patient characteristics

One potential source of heterogeneity in VTE incidence studies are differences in patient characteristics across studies. These patient characteristics are factors that increase or decrease risk of VTE, for example, established risk factors such as age and comorbidities²⁸ or ethnicity.²⁹ For example, Mei et al.³⁰ performed a study among

FIGURE 1 Clinical sources of heterogeneity in venous thromboembolism incidence studies that may explain observed heterogeneity across studies. Abbreviations: ICU, intensive care unit; OAC, oral anticoagulation; VTE, venous thromboembolism



subjects with a mean age of 55.5 years (range, 0.5–87), of whom 0.8% had a history of VTE. They reported a VTE incidence of 2.0% (95% CI, 0.3–3.6). In contrast, Middeldorp et al.³¹ reported a VTE incidence of 19.7% (95% CI, 14.2–25.2) in a patient group that was older (mean age, 61 years; standard deviation [SD], 4) and in whom a history of VTE was more frequent (5.6%). Hence, the underlying VTE risk may have been higher in the latter study, which may be one of the factors explaining the higher VTE incidence found in that study.

In addition to patient profiles, also relevant are characteristics of the research setting, related to COVID-19 disease severity or VTE risk. For example, critically ill patients are at higher risk of developing VTE compared to non-ICU patients,³² so inclusion of patients from the ICU, the general ward, or both affects VTE incidence. In the study by Al-Samkari et al.,³³ patients from both the general ward and ICU were included. In their study, a VTE incidence of 3.1% (95% CI, 1.0–5.3) was found in ward patients and a VTE incidence of 7.6% (95% CI, 3.3–12.0) in ICU patients. Of note, the case mix of patients with COVID-19 in the ICU may differ between countries due to national-level differences in accessibility of ICU beds.³⁴ What is more, VTE incidence in outpatients with COVID-19 is different from VTE incidence in hospitalized patients with COVID-19.³⁵ Furthermore, limiting or *not* limiting the research setting to patients with, for example, an elevated D-dimer level may affect VTE incidence, because patients with an elevated D-dimer level are at high risk of developing VTE.²⁰ For example, Demelo-Rodríguez et al.³⁶ included only patients with a D-dimer level >1000 ng/ml and reported a VTE incidence of 14.7% (95% CI, 9.2–20.3). In comparison, Whyte et al.³⁷ did not use a D-dimer level threshold to restrict patient inclusion and included *all* hospitalized patients with COVID-19 and found a VTE incidence of 5.4% (95% CI, 4.3–6.6). In addition, the way in which patient selection was performed may affect the research setting and, consequently, VTE risk. For example, in a study by Hill et al.,³⁸ a VTE incidence of 1.4% (95% CI, 1.1–1.7) was found. In this study, patients were included retrospectively, by screening electronic health records and including all patients positive for SARS-CoV-2 on polymerase chain reaction-based testing. Patients were

included after a visit to an emergency department and/or admission to an inpatient unit. In comparison, in a study by Trimaille et al.,³⁹ a VTE incidence of 17.0% (95% CI, 12.6–21.3) was found. In this study, all consecutive patients hospitalized for COVID-19 were included. In these two studies, the clinical characteristics of the underlying populations from which the study populations were sampled were different, which may have affected baseline risk for VTE.

A third characteristic that requires attention is the local medical strategy, such as the use of anticoagulation treatment or COVID-19 treatment, which may influence the risk of VTE. For example, a patient group treated with full-dose anticoagulation may show a lower VTE incidence compared to patient groups receiving no or prophylactic anticoagulation. Cattaneo et al. reported a VTE incidence of 0.0% (95% CI 0.000; 0.008). In this study, all patients had been treated with standard dose thromboprophylaxis.⁴⁰ In comparison, Zhang et al. reported a VTE incidence of 46.2% (95% CI 38.0; 54.3). In this study, 90 patients out of 143 patients (63%) received no anticoagulation.⁴¹ The difference in VTE incidence between these two studies could be partly explained by the difference in use of anticoagulation. Additionally, as of 2 September 2020, the WHO recommended the use of systemic corticosteroids in patients with severe or critical COVID-19.^{42–44} Corticosteroids may interfere with VTE incidence. For example, this meta-analysis showed an increased risk of 1.39 (95% CI 1.10–1.77) of VTE when being administered corticosteroids.⁴⁵ The use of corticosteroids may therefore also be a source of heterogeneity in VTE incidence.

3.1.2 | VTE testing

An additional clinical source of heterogeneity in VTE incidence is variation in VTE diagnostic practices. In particular, reasons to test for VTE and reasons to *not* test for VTE differed across studies. For example, diagnostic tests for PE or DVT may have been conducted in case of symptoms. Alternatively, a patient may have been tested for VTE independent of symptoms (i.e., screening), detecting

both symptomatic and asymptomatic cases. For example, Cattaneo et al.⁴⁰ found no symptomatic DVT cases in their study, resulting in a VTE incidence of 0.0% (95% CI, 0.000–0.008). In comparison, Demelo-Rodríguez et al.³⁶ screened for asymptomatic DVT and found an incidence of 14.7% (95% CI, 9.2–20.3). Furthermore, studies may use a decision rule (e.g., based on lab results) before undertaking imaging. For example, Whyte et al.³⁷ found a VTE incidence of 5.4% (95% CI, 4.3–6.6). In this study, imaging was not undertaken “for those considered ‘PE unlikely’ by the Wells score (score <4) in conjunction with a D-dimer result below 500 ng/ml.” In comparison, Voicu et al.⁴⁶ performed ultrasound imaging in *all* patients 3 days after intubation and found a VTE incidence of 35.7% (95% CI, 23.2–48.3). Studies using a decision rule for VTE imaging may miss cases of VTE⁴⁷ but are a closer resemblance of clinical practice. What is more, despite a VTE testing protocol being in place, VTE testing may not be reasonable or feasible in some patients, and studies may therefore deviate from their testing protocol in some cases. For example, VTE testing may not be reasonable in patients hospitalized for palliative care, and VTE testing may not be feasible due to limitations in (human) resources in a health crisis setting, since performing a computed tomographic pulmonary angiogram (CTPA) in an ICU patient with mechanical ventilation can be laborious. For instance, Koleilat et al.⁴⁸ reported a VTE incidence of 0.5% (95% CI, 0.3–0.8). In this study, only “those patients with significant clinical concern for DVT or in those in whom the results were deemed to impact management were tested for DVT (e.g., patients who were mechanically ventilated and placed prone for persistently poor oxygenation were deemed too unstable, and those already on anticoagulation for other reasons such as cardiac arrhythmias or a prior history of thrombotic episodes requiring lifelong anticoagulation were unlikely to undergo venous duplex testing).” In comparison, Ren et al.⁴⁹ reported a (both a symptomatic and asymptomatic) VTE incidence of 85.4% (95% CI, 75.4–95.4). In the latter study, *all* patients were tested for DVT at least twice.

3.2 | Methodologic sources

3.2.1 | VTE end point

Heterogeneity in VTE incidence studies may be caused by inconsistent inclusion of types of VTE across studies. For example, Mazzaccaro et al.⁵⁰ reported a VTE incidence of 65.6% (95% CI, 49.2%–82.1%), where VTE included pulmonary embolism, diagnosed using a CTPA, or DVT, which was diagnosed with an ultrasound of the veins of the upper and lower limbs. In contrast, the study by Criel et al.⁵¹ reported a VTE incidence of 7.3% (95% CI, 1.7–13.0). Here, VTE included DVT only. Furthermore, thrombosis in other venous compartments may be included (e.g., upper extremity, splanchnic veins). In the above-mentioned study by Mazzaccaro et al.,⁵⁰ all patients underwent a duplex scan of the veins and arteries of the *upper and lower* limbs to investigate the presence of peripheral thrombosis. In contrast, Santoliquido et al.⁵² reported a VTE incidence

of 11.9% (95% CI, 5.0–18.8). Here, all patients were screened for DVT with *lower-limb* venous compression ultrasound. Another example is the study by Llitjos et al.⁵³ which found a VTE incidence of 69.2% (95% CI, 51.5–87.0) in which 4 of 18 (22%) reported DVTs were superficial. In comparison, the study by Desborough et al. did not include superficial DVTs and found a VTE incidence of 15.2% (95% CI, 6.5–23.8).⁵⁴ In addition, a distinction can be made between central, segmental, and subsegmental PEs, based on the location of thrombi in the pulmonary vascular tree. Longchamp et al.⁵⁵ “did not record subsegmental PEs” and reported a VTE incidence of 56.0% (95% CI, 36.5–75.5). In comparison, Mazzaccaro et al.⁵⁰ found a VTE incidence of 65.6% (95% CI, 49.2–82.1), based on 21 cases of “pulmonary vessel thrombosis,” including 7 (33.3%) cases of subsegmental thrombi. Additionally, DVT may be associated with indwelling lines, and these DVTs could be included or not. For example, in the study by Desborough et al.⁵⁴ 10 of the 66 patients were diagnosed with VTE, resulting in a VTE incidence of 15.2% (95% CI, 6.5–23.8). However, six of the DVTs were found to be associated with a line, and one patient had both a DVT and a PE. Consequently, five patients had a non-line-associated VTE, changing VTE incidence to 7.6% (95% CI, 1.2–14.0).

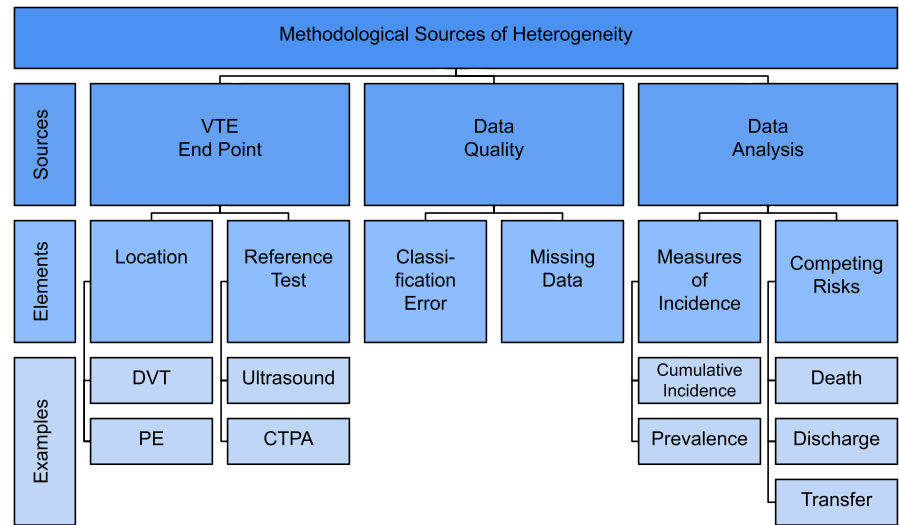
VTE end point classification may also differ across studies in terms of the protocol that was used for the interpretation of the computed tomography (CT) or ultrasound test by radiologists for a VTE diagnosis. Chen et al.⁵⁶ reported a VTE incidence of 1% (95% CI, 0.4–1.6). In this study, “all CT and CTPA image analyses were performed by 2 radiologists experienced in thoracic radiology [...], who were blinded to the clinical information. Disagreements were resolved through discussion until consensus was reached.” Conversely, Artifoni et al.⁵⁷ reported a VTE incidence of 22.5% (95% CI, 12.8–32.3) in a study where “chest angio-CT scan was performed in case of suspicion of pulmonary embolism.” In the study by Chen et al., classification error in VTE diagnosis is less likely, while the study by Artifoni et al. more closely resembles clinical practice.

In addition, a potential source of heterogeneity in the VTE end point across studies is the data source used to classify the VTE end point. Data quality may differ between data sources, which is discussed in the subsequent subsection.

3.2.2 | Data quality

A potential source of heterogeneity in VTE incidence studies is classification error or missing data in the VTE end point or in SARS-CoV-2 infection status. Thirty-four of the 49 VTE incidence studies (69%) included in the meta-analysis by Jiménez et al.²⁷ were identified as retrospective studies, 11 (22%) were identified as prospective studies, and 4 (8%) as cross-sectional studies. In the 34 retrospective studies, data were often not primarily collected to study VTE incidence, which increases the potential risk for incorrectness of VTE end point classification and SARS-CoV-2 infection (i.e., a false-positive or false-negative diagnosis). Classification error occurs, for

FIGURE 2 Methodological sources of heterogeneity in venous thromboembolism incidence studies that may explain observed heterogeneity across studies. Abbreviations: CTPA, computed tomography pulmonary angiogram; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism



example, due to an incorrect interpretation of a radiologist or errors in data extraction and entering in databases. Specifically, in the study by Hill et al.,³⁸ reporting a VTE incidence of 3.1% (95% CI, 2.5–3.8), electronic health records were queried to identify patients with a diagnosis of VTE. Patients were identified as cases when they received apixaban, rivaroxaban, or dabigatran. Consequently, classification error in the VTE end point may be more likely in the study by Hill et al. than in a study using clinical radiology reports for VTE end point classification. Radiology reports were used in the study by Chen et al.,⁵⁶ for example, reporting a VTE incidence of 1.0% (95% CI, 0.4–1.6).

The consequences of classification error and missing data in SARS-CoV-2 infection status are illustrated by the VTE incidence study conducted by Koleilat et al.⁴⁸ In the meta-analysis by Jiménez et al.,²⁷ a VTE incidence of 0.5% (95% CI, 0.3–0.8) was reported for the study by Koleilat et al. This number was calculated by dividing the number of patients with a DVT diagnosis (18) by the number of patients admitted to the hospital with “confirmed COVID-19” (3404). It is unknown what was meant by “confirmed COVID-19” in the original article. The flowchart published by Koleilat et al. shows that of the 3404 patients with “confirmed COVID-19,” 846 patients underwent lower-extremity venous duplexes, of whom 145 patients tested SARS-CoV-2 negative, 135 patients tested SARS-CoV-2 positive, and 566 were not tested for SARS-CoV-2. Koleilat et al. did not report the SARS-CoV-2 status of the remaining 2558 patients that did not undergo lower-extremity venous duplexes. Consequently, due to missing data in SARS-CoV-2 infection status, and potential classification error in the “confirmed COVID-19” cases, it is unknown what the correct estimate for VTE incidence was in this study. As an example, if VTE incidence calculation had been restricted to those patients who were known to be tested SARS-CoV-2 positive (135), VTE incidence would change dramatically to 18 of 135 (13.3%; 95% CI, 7.6–19.1).

Another example of the consequences of missing data in VTE diagnosis is the VTE incidence study conducted by Chen et al.⁵⁶ In this study, 1008 patients were hospitalized with COVID-19-associated

pneumonia. A VTE was diagnosed in 10 patients, and consequently the meta-analysis by Jiménez et al.²⁷ reported a VTE incidence of 1.0% (95% CI, 0.4–1.6). In the analysis reported in the original paper, all patients were excluded who did not undergo CTPA examination, since these patients had missing data in VTE diagnosis (yes/no). Restricting the analysis to these 25 patients would change VTE incidence dramatically to 40.0% (95% CI, 20.8–59.2). Including or excluding the patients not undergoing VTE testing, changes the research setting of a study (see also section 3.1.1), particularly because, most likely, the odds of a VTE was a priori lower in the group not undergoing a CTPA, compared with the group undergoing a CTPA, which was performed only in patients with “elevated D-dimer level or accompanying symptom(s), including chest pain, hemoptysis, and dyspnea.”⁵⁶

3.2.3 | Data analysis

The frequency measures used to describe VTE incidence may also differ across studies, possibly contributing to heterogeneity in VTE incidence. Commonly used, yet distinct, measures include the cumulative incidence (or risk or incidence proportion), the prevalence, and incidence rate.

The risk (or cumulative incidence) is the probability of getting a VTE in a certain period of time and is calculated by dividing the number of subjects who experienced the outcome in a certain time period by the total number of subjects that were observed during that time period.⁵⁸ Estimating this measure requires that patients are followed for the entire time period. In addition, interpretation of a risk is warranted only when the length of the time period over which the risk applies is known, which should therefore be reported. When the time period is small, VTE incidence would approach zero, whereas as the time period becomes longer, VTE incidence will increase.⁵⁹ Whyte et al.³⁷ reported a cumulative incidence at 24 h of 2.1% (95% CI, 1.4–2.8). In comparison, Middeldorp et al.³¹ reported cumulative incidences of VTE

at 7 days, 14 days, and 21 days of 16% (95% CI, 10–22), 33% (95% CI, 23–43) and 42% (95% CI, 30–54), respectively. Since follow-up duration was highly variable in general, proper interpretation of the reported risks is a challenge and forms a possible explanation for the heterogeneity in VTE incidence.

Prevalence is defined as the proportion of COVID-19 patients with VTE at a particular moment in time.⁵⁸ In a cross-sectional study conducted by Criel et al.,⁵¹ 82 patients were included and consecutively screened for VTE. In this study, the patients were not followed over time, and consequently this study estimated VTE prevalence rather than incidence, which was found to be 7.3% (95% CI, 1.7–13.0). In comparison, Desborough et al.⁵⁴ followed patients for 28 days after admission to critical care (or until death) and reported a VTE incidence of 15.2% (95% CI, 6.5–23.8). These two estimates are heterogeneous since VTE prevalence (Criel et al.) and VTE incidence (Desborough et al.) are incomparable.

Another measure of VTE incidence is the VTE incidence rate, which explicitly takes the duration of follow-up into account. It can be calculated by dividing the number of patients with COVID-19 who developed VTE by the total amount of time those patients were followed. For example, Klok et al.² reported a VTE incidence rate of 13 per patient-year (95% CI, 6–27). This method implicitly takes the length of the follow-up period and variations between patients into account.

Another source of heterogeneity across studies is how *competing risks* are handled in the analysis. In VTE studies of COVID-19, patients can develop a VTE, die, be discharged from the hospital, or be transferred to another hospital. It is often not known whether these patients developed a VTE after discharge or hospital transfer, and it is impossible to know whether these patients would have developed a VTE if they had not died. Moreover, if a patient dies, autopsy should be performed to identify whether the cause of death was a VTE, which usually does not happen. In these patients, the VTE end point may, therefore, be misclassified (false negative). For example, Middeldorp et al.³¹ reported, “We did not adjudicate deaths to identify fatal PE because almost all deaths were due to hypoxemic respiratory failure, which can be indistinguishable from fatal PE, whereas autopsies were rarely performed in COVID-19 patients.” Adjusting or *not* adjusting for competing risks affects the reported cumulative incidence. Klok et al.² reported a crude cumulative incidence of 57% (95% CI, 47–67) and a cumulative incidence adjusted for the competing risk of death of 49% (95% CI, 41–57). A cumulative incidence adjusted for the competing risk of death *and* hospital discharge may have decreased the cumulative incidence further since 43% of the patients included in the study were discharged alive.

4 | DISCUSSION

Studies on VTE incidence in patients with COVID-19 show highly heterogeneous results. We identified different sources of this phenomenon, notably, clinical and methodological sources, and

illustrated these using various examples. The list of sources of heterogeneity in VTE incidence studies described here (characteristics of study participants, VTE testing, VTE end point, data quality, and data analysis) is not exhaustive, and more aspects may be needed to fully comprehend the heterogeneity across studies. Nevertheless, we consider these sources to be important explanations, and we, therefore, feel that reporting of these aspects in future VTE incidence studies is required to appreciate and to properly interpret reported VTE incidences. A list of these suggestions is provided in [Table 1](#).

We discussed individual sources of heterogeneity in VTE incidence, but obviously these could occur simultaneously. When two studies differ regarding multiple sources of heterogeneity, the difference in VTE incidence could increase, but it could also lead to a cancellation of effects. We do not mean to suggest that the differences in VTE incidence in our examples are caused by the discussed sources of heterogeneity. We solely provide one of the many explanations for a difference in VTE incidence. The example studies referenced in this article are merely illustrations and do not reflect our view about their quality.

The heterogeneity in reports of VTE incidence not only complicates interpretation of VTE incidence but may also affect trials using VTE incidence as the primary end point or one of the secondary end points, such as trials comparing different thromboprophylaxis strategies in patients with COVID-19. Specifically, the sample size of these trials may be based on a reported VTE incidence, which may not reflect VTE incidence in the research setting of the trial, leading to an under- or overpowered study. For example, the study by Connors et al.,³⁵ studying the effect of antithrombotic therapy on clinical outcomes in outpatients, “was terminated because of a control event rate lower than anticipated.” It is unclear if sample size calculation was directly affected by studies reporting high VTE incidence in (ambulatory) patients with COVID-19. Connors et al. assumed a placebo event rate of 8% as “previous trials of anticoagulants for prevention of thrombotic events in ambulatory patients have noted similar event rates.” What is more, most, if not all, aspects described in this paper translate to trial settings. For example, if no clear and unambiguous description is provided of VTE end point assessment in trials, estimates of treatment effect (e.g., risk difference), or the number needed to treat derived from it, cannot be interpreted.

Standardizing VTE research is not limited to COVID-19. Several efforts have already been made to improve the quality and consistency of VTE clinical research data and reporting practices. Examples include, among others, the VTE Common Data Elements project launched in November 2018 by the ISTH⁶⁰ and recommendations for standardized reporting and analysis of VTE in oncology trials.⁶¹

Standardizing reports of VTE incidence studies is important and allows for comparisons of VTE incidence across groups (e.g., hospitals, countries, regions, sex, or over time), across diseases (e.g., influenza), and for better understanding and comparison of the results of trials on treatments aimed at reducing VTE incidence.

TABLE 1 Suggestions for reporting of studies on incidence of VTE in patients with COVID-19

Sources of heterogeneity	Element	Reporting suggestions
Clinical sources	Characteristics of study participants	Describe the patient profiles (e.g., sex, age, comorbidities) Describe the research setting (e.g., ICU, ward) Describe the patients' medical treatments (e.g., anticoagulation, steroids)
	VTE testing	Describe the VTE testing protocol (e.g., screening, symptoms, testing based on lab results) Describe the reasons to deviate from the VTE testing protocol (e.g., when testing was not reasonable, palliative care) or feasible (e.g., limited [human] resources or when testing had no clinical consequences)
Methodological sources	VTE end point	Describe the types of VTE that were included (e.g., pulmonary embolism, deep vein thrombosis) Describe the reference test used (e.g., ultrasound, computed tomographic pulmonary angiogram)
	Data quality	Describe the likelihood of classification errors and its consequences (e.g., classification error in VTE diagnosis and SARS-CoV-2 infection) Describe missing data and its consequences (e.g., missing data in VTE diagnosis and SARS-CoV-2 infection)
	Data analysis	Describe the measure of incidence used and report its unit (if applicable) (e.g., cumulative incidence, prevalence) Describe competing risks (e.g., death, discharge, transfer)

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VTE, venous thromboembolism.

Careful description of the elements affecting heterogeneity in future VTE incidence studies may better isolate important differences across groups, diseases, and treatments and allow meta-analyses that provide summary results based on more homogeneous studies. Eventually, such literature will contribute to improved management of VTE risk in patients with COVID-19.

AUTHOR CONTRIBUTIONS

LN, RHHG, and SCC conceptualized and designed the study. LN wrote the manuscript critically, which was subsequently revised by RHHG, BSB, FAK, MJHAK, and SCC. All authors approved the final manuscript for publication.

ACKNOWLEDGMENTS

The authors thank the Dutch COVID & Thrombosis Coalition for the internal discussions that shaped this project. Our acknowledgement does not mean their endorsement.

FUNDING INFORMATION

This study was supported by grants from the Netherlands Thrombosis Foundation (2020_A) and the Netherlands Organization for Health Research and Development (project number 10430012010004).

RELATIONSHIP DISCLOSURE

FAK has received research support from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, MSD, Daiichi-Sankyo, Actelion, the Dutch Thrombosis Association, the Netherlands Organization for Health Research and Development, and the Dutch Heart foundation.

MJHAK has received an unrestricted grant (outside this work) from Sobi; payment to the Erasmus Medical Center; and speakers fee from Sobi, Roche, and Bristol-Myers Squibb, payment to the institute. LN, RHHG, BSB, and SCC declare no conflicts of interest.

ORCID

Linda Nab  <https://orcid.org/0000-0002-1821-7246>

Rolf H. H. Groenwold  <https://orcid.org/0000-0001-9238-6999>

Frederikus A. Klok  <https://orcid.org/0000-0001-9961-0754>

Soerajja Bhoelan  <https://orcid.org/0000-0002-5205-5738>

Marieke J. H. A. Kruip  <https://orcid.org/0000-0002-0265-4871>

Suzanne C. Cannegieter  <https://orcid.org/0000-0003-4707-2303>

TWITTER

Linda Nab  @lindanab1

Rolf H. H. Groenwold  @ProfGroenwold

Frederikus A. Klok  @Erik_Klok_MD

Suzanne C. Cannegieter  @s_cannegieter

REFERENCES

1. Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med*. 2021;9(6):622-642.
2. Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. *Thromb Res*. 2020;191:148-150.
3. Al-Ani F, Chehade S, Lazo-Langner A. Thrombosis risk associated with COVID-19 infection. A scoping review. *Thromb Res*. 2020;192:152-160.

4. Birocchi S, Manzoni M, Podda GM, Casazza G, Cattaneo M. High rates of pulmonary artery occlusions in COVID-19. A meta-analysis. *Eur J Clin Invest*. 2021;51(1):e13433. doi:10.1111/eci.13433
5. Kollias A, Kyriakoulis KG, Lagou S, Kontopantelis E, Stergiou GS, Syrigos K. Venous thromboembolism in COVID-19: a systematic review and meta-analysis. *Vasc Med*. 2021;26(4):415-425. doi:10.1177/1358863X21995566
6. Kunutsor SK, Laukkanen JA. Incidence of venous and arterial thromboembolic complications in COVID-19: a systematic review and meta-analysis. *Thromb Res*. 2020;196:27-30.
7. Liu Y, Cai J, Wang C, Jin J, Qu L. Incidence, prognosis, and laboratory indicators of venous thromboembolism in hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. *J Vasc Surg Venous Lymphat Disord*. 2021;9(5):1099-1111.e6.
8. Longchamp G, Manzocchi-Besson S, Longchamp A, Righini M, Robert-Ebadi H, Blondon M. Proximal deep vein thrombosis and pulmonary embolism in COVID-19 patients: a systematic review and meta-analysis. *Thromb J*. 2021;19(1):15. doi:10.1186/s12959-021-00266-x
9. Lu Y, Pan L, Zhang W-W, et al. A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19. *Int J Infect Dis*. 2020;100:34-41.
10. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. *EClinicalMedicine*. 2020;29:100639.
11. Mohamed MFH, Al-Shokri SD, Shunnar KM, et al. Prevalence of venous thromboembolism in critically ill COVID-19 patients: systematic review and meta-analysis. *Front Cardiovasc Med*. 2021;7:598846. doi:10.3389/fcvm.2020.598846/full
12. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Res Pract Thromb Haemost*. 2020;4(7):1178-1191. doi:10.1002/rth2.12439
13. Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AWS, Di Nisio M. Venous thromboembolism in patients with COVID-19: systematic review and meta-analysis. *Thromb Res*. 2020;196:67-74.
14. Sridharan GK, Vegunta R, Rokkam VRP, et al. Venous thromboembolism in hospitalized COVID-19 patients. *Am J Ther*. 2020;27(6):e599-e610. doi:10.1097/MJT.0000000000001295
15. Boonyawat K, Chantrathammachart P, Numthavaj P, et al. Incidence of thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Thromb J*. 2020;18(1):34. doi:10.1186/s12959-020-00248-5
16. Tan BK, Mainbourg S, Friggeri A, et al. Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis. *Thorax*. 2021;76(10):970-979. doi:10.1136/thoraxjnl-2020-215383
17. Wu C, Liu Y, Cai X, Zhang W, Li Y, Fu C. Prevalence of venous thromboembolism in critically ill patients with coronavirus disease 2019: a meta-analysis. *Front Med*. 2021;29:8. doi:10.3389/fmed.2021.603558/full
18. Wu T, Zuo Z, Yang D, et al. Venous thromboembolic events in patients with COVID-19: a systematic review and meta-analysis. *Age Ageing*. 2021;50(2):284-293.
19. Zhang C, Shen L, Le K-J, et al. Incidence of venous thromboembolism in hospitalized coronavirus disease 2019 patients: a systematic review and meta-analysis. *Front Cardiovasc Med*. 2020;6:7. doi:10.3389/fcvm.2020.00151/full
20. Zhan H, Chen H, Liu C, et al. Diagnostic value of D-dimer in COVID-19: a meta-analysis and meta-regression. *Clin Appl Thromb*. 2021;27:10760296211010976. doi:10.1177/10760296211010976
21. Chi G, Lee JJ, Jamil A, et al. Venous thromboembolism among hospitalized patients with COVID-19 undergoing thromboprophylaxis: a systematic review and meta-analysis. *J Clin Med*. 2020;9(8):2489.
22. Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and venous thromboembolism: a meta-analysis of literature studies. *Semin Thromb Hemost*. 2020;46(7):763-771. doi:10.1055/s-0040-1715456
23. Gallastegui N, Zhou JY, von Drygalski A, Barnes RFW, Fernandes TM, Morris TA. Pulmonary embolism does not have an unusually high incidence among hospitalized COVID-19 patients. *Clin Appl Thromb*. 2021;27:1076029621996471. doi:10.1177/1076029621996471
24. Giustozzi M, Vedovati MC, Agnelli G. Venous thromboembolism and COVID-19: mind the gap between clinical epidemiology and patient management. *Eur J Intern Med*. 2020;82:18-20.
25. Gratz J, Wiegeler M, Maleczek M, et al. Risk of clinically relevant venous thromboembolism in critically ill patients with COVID-19: a systematic review and meta-analysis. *Front Med*. 2021;9:8. doi:10.3389/fmed.2021.647917/full
26. Hasan SS, Radford S, Kow CS, Zaidi STR. Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: a systematic review and meta-analysis. *J Thromb Thrombolysis*. 2020;50(4):814-821. doi:10.1007/s11239-020-02235-z
27. Jiménez D, García-Sánchez A, Rali P, et al. Incidence of VTE and bleeding among hospitalized patients with coronavirus disease 2019. *Chest*. 2021;159(3):1182-1196.
28. Cushman M. Epidemiology and risk factors for venous thrombosis. *Semin Hematol*. 2007;44(2):62-69.
29. Liao S, Woulfe T, Hyder S, Merriman E, Simpson D, Chunilal S. Incidence of venous thromboembolism in different ethnic groups: a regional direct comparison study. *J Thromb Haemost*. 2014;12(2):214-219. doi:10.1111/jth.12464
30. Mei F, Fan J, Yuan J, et al. Comparison of venous thromboembolism risks between COVID-19 pneumonia and community-acquired pneumonia patients. *Arterioscler Thromb Vasc Biol*. 2020;40(9):2332-2337. doi:10.1161/ATVBAHA.120.314779
31. Middeldorp S, Coppens M, Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020;18(8):1995-2002. doi:10.1111/jth.14888
32. Minet C, Potton L, Bonadona A, et al. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. *Crit Care*. 2015;19(1):287.
33. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*. 2020;136(4):489-500.
34. Bauer J, Brüggemann D, Klingelhöfer D, et al. Access to intensive care in 14 European countries: a spatial analysis of intensive care need and capacity in the light of COVID-19. *Intensive Care Med*. 2020;46(11):2026-2034. doi:10.1007/s00134-020-06229-6
35. Connors JM, Brooks MM, Sciruba FC, et al. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19. *JAMA*. 2021;326(17):1703-1712.
36. Demelo-Rodríguez P, Cervilla-Muñoz E, Ordieres-Ortega L, et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. *Thromb Res*. 2020;192:23-26.
37. Whyte MB, Kelly PA, Gonzalez E, Arya R, Roberts LN. Pulmonary embolism in hospitalised patients with COVID-19. *Thromb Res*. 2020;195:95-99.
38. Hill JB, Garcia D, Crowther M, et al. Frequency of venous thromboembolism in 6513 patients with COVID-19: a retrospective study. *Blood Adv*. 2020;4(21):5373-5377.
39. Trimaille A, Curtiaud A, Marchandot B, et al. Venous thromboembolism in non-critically ill patients with COVID-19 infection. *Thromb Res*. 2020;193:166-169.
40. Cattaneo M, Bertinato EM, Birocchi S, et al. Pulmonary embolism or pulmonary thrombosis in COVID-19? Is the recommendation to use high-dose heparin for thromboprophylaxis justified? *Thromb Haemost*. 2020;120(8):1230-1232. doi:10.1055/s-0040-1712097

41. Zhang L, Feng X, Zhang D, et al. Deep vein thrombosis in hospitalized patients with COVID-19 in Wuhan, China. *Circulation*. 2020;142(2):114-128. doi:10.1161/CIRCULATIONAHA.120.046702
42. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(8):693-704. doi:10.1056/NEJMoa2021436
43. Agarwal A, Rochweg B, Siemieniuk RA, et al. A living WHO guideline on drugs for COVID-19. *BMJ*. 2020;370:m3379. doi:10.1136/bmj.m3379
44. WHO. Therapeutics and COVID-19: living guideline [Internet]. 2021 [cited 2021 Jul 23]. Available from: <https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2>
45. Sarfraz A, Sarfraz Z, Razzack AA, Patel G, Sarfraz M. Venous thromboembolism, corticosteroids and COVID-19: a systematic review and meta-analysis. *Clin Appl Thromb Hemost*. 2021;27:1076029621993573. doi:10.1177/1076029621993573
46. Voicu S, Bonnin P, Stépanian A, et al. High prevalence of deep vein thrombosis in mechanically ventilated COVID-19 patients. *J Am Coll Cardiol*. 2020;76(4):480-482.
47. Stals MAM, Kaptein FHJ, Bemelmans RHH, et al. Ruling out pulmonary embolism in patients with (suspected) COVID-19—a prospective cohort study. *TH Open*. 2021;5(3):e387-e399. doi:10.1055/s-0041-1735155
48. Koleilat I, Galen B, Choinski K, et al. Clinical characteristics of acute lower extremity deep venous thrombosis diagnosed by duplex in patients hospitalized for coronavirus disease 2019. *J Vasc Surg Venous Lymphat Disord*. 2021;9(1):36-46.
49. Ren B, Yan F, Deng Z, et al. Extremely high incidence of lower extremity deep venous thrombosis in 48 patients with severe COVID-19 in Wuhan. *Circulation*. 2020;142(2):181-183. doi:10.1161/CIRCULATIONAHA.120.047407
50. Mazzaccaro D, Giacomazzi F, Giannetta M, et al. Non-overt coagulopathy in non-ICU patients with mild to moderate COVID-19 pneumonia. *J Clin Med*. 2020;9(6):1781.
51. Criel M, Falter M, Jaeken J, et al. Venous thromboembolism in SARS-CoV-2 patients: only a problem in ventilated ICU patients, or is there more to it? *Eur Respir J*. 2020;56:2001201. doi:10.1183/13993003.01201-2020
52. Santoliquido A, Porfidia A, Nesci A, et al. Incidence of deep vein thrombosis among non-ICU patients hospitalized for COVID-19 despite pharmacological thromboprophylaxis. *J Thromb Haemost*. 2020;18(9):2358-2363. doi:10.1111/jth.14992
53. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost*. 2020;18:1743-1746. doi:10.1111/jth.14869
54. Desborough MJR, Doyle AJ, Griffiths A, Retter A, Breen KA, Hunt BJ. Image-proven thromboembolism in patients with severe COVID-19 in a tertiary critical care unit in the United Kingdom. *Thromb Res*. 2020;193:1-4.
55. Longchamp A, Longchamp J, Manzocchi-Besson S, et al. Venous thromboembolism in critically ill patients with COVID-19: results of a screening study for deep vein thrombosis. *Res Pract Thromb Haemost*. 2020;4(5):842-847. doi:10.1002/rth2.12376
56. Chen J, Wang X, Zhang S, et al. Characteristics of acute pulmonary embolism in patients with COVID-19 associated pneumonia from the city of Wuhan. *Clin Appl Thromb*. 2020;1(26):1-8. doi:10.1177/1076029620936772
57. Artifoni M, Danic G, Gautier G, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. *J Thromb Thrombolysis*. 2020;50(1):211-216. doi:10.1007/s11239-020-02146-z
58. Rothman KJ. *Epidemiology: an Introduction*. Oxford University Press; 2002.
59. Morgenstern H, Kleinbaum DG, Kupper LL. Measures of disease incidence used in epidemiologic research. *Int J Epidemiol*. 1980;9(1):97-104. doi:10.1093/ije/9.1.97
60. Le Gal G, Carrier M, Castellucci LA, et al. Development and implementation of common data elements for venous thromboembolism research: on behalf of SSC subcommittee on official communication from the SSC of the ISTH. *J Thromb Haemost*. 2021;19(1):297-303. doi:10.1111/jth.15138
61. Carrier M, Khorana AA, Zwicker JI, Lyman GH, Le Gal G, Lee AYY. Venous thromboembolism in cancer clinical trials: recommendation for standardized reporting and analysis. *J Thromb Haemost*. 2012;10(12):2599-2601. doi:10.1111/jth.12028

How to cite this article: Nab L, Groenwold RHH, Klok FA, Bhoelan S, Kruij MJH, Cannegieter SC. Estimating incidence of venous thromboembolism in COVID-19: Methodological considerations. *Res Pract Thromb Haemost*. 2022;6:e12776. doi: [10.1002/rth2.12776](https://doi.org/10.1002/rth2.12776)