Original Article

SARS-CoV-2 infection and venous thromboembolism after surgery: an international prospective cohort study

COVIDSurg Collaborative* and **GlobalSurg Collaborative***

NIHR Global Health Research Unit on Global Surgery, Birmingham, UK

Summary

SARS-CoV-2 has been associated with an increased rate of venous thromboembolism in critically ill patients. Since surgical patients are already at higher risk of venous thromboembolism than general populations, this study aimed to determine if patients with peri-operative or prior SARS-CoV-2 were at further increased risk of venous thromboembolism. We conducted a planned sub-study and analysis from an international, multicentre, prospective cohort study of elective and emergency patients undergoing surgery during October 2020. Patients from all surgical specialties were included. The primary outcome measure was venous thromboembolism (pulmonary embolism or deep vein thrombosis) within 30 days of surgery. SARS-CoV-2 diagnosis was defined as peri-operative (7 days before to 30 days after surgery); recent (1–6 weeks before surgery); previous (≥7 weeks before surgery); or none. Information on prophylaxis regimens or pre-operative anti-coagulation for baseline comorbidities was not available. Postoperative venous thromboembolism rate was 0.5% (666/123,591) in patients without SARS-CoV-2; 2.2% (50/2317) in patients with peri-operative SARS-CoV-2; 1.6% (15/953) in patients with recent SARS-CoV-2; and 1.0% (11/1148) in patients with previous SARS-CoV-2. After adjustment for confounding factors, patients with peri-operative (adjusted odds ratio 1.5 (95%CI 1.1–2.0)) and recent SARS-CoV-2 (1.9 (95%CI 1.2–3.3)) remained at higher risk of venous thromboembolism, with a borderline finding in previous SARS-CoV-2 (1.7 (95%CI 0.9–3.0)). Overall, venous thromboembolism was independently associated with 30-day mortality (5.4 (95%CI 4.3–6.7)). In patients with SARS-CoV-2, mortality without venous thromboembolism was 7.4% (319/4342) and with venous thromboembolism was 40.8% (31/76). Patients undergoing surgery with peri-operative or recent SARS-CoV-2 appear to be at increased risk of postoperative venous thromboembolism compared with patients with no history of SARS-CoV-2 infection. Optimal venous thromboembolism prophylaxis and treatment are unknown in this cohort of patients, and these data should be interpreted accordingly.

Correspondence to: E. Li
Email: elizabeth.li@nhs.net
Accepted: 20 July 2021
Keywords: COVID-19; deep vein thrombosis; pulmonary embolism; SARS-CoV-2; venous thromboembolism
*Collaborating authors are listed in online Supporting Information Appendix S1.
This article is accompanied by an editorial by Marshall and Duggan. *Anaesthesia* 2022; **77**: 3–6.
Twitter: @CovidSurg; @GlobalSurg

Introduction

Patients hospitalised with COVID-19 have a high risk of venous thromboembolism (VTE), with an estimated incidence between 9% and 26% [1–5] despite pharmacological prophylaxis, and as high as 21–31% in patients within critical care settings [1, 2, 4, 6]. As a result, preliminary mixed guidance has been issued, with some suggesting no change in practice, while others suggesting that increased doses and duration of pharmacological prophylaxis may be beneficial [7, 8]. However, such

© 2021 The Authors. *Anaesthesia* published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists.
This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

regimens are associated with serious bleeding risks [9]. Determining the optimal VTE prophylactic regimen for patients with moderate and severe COVID-19 is an active area of research (e.g. REMAP-CAP, ACTIV-4a, ATTACC Investigators, pre-print, https://doi.org/10.1101/2021.03.10.21252749) [10].

The incidence of VTE in surgical patients infected with SARS-CoV-2 is not well known. Most patients undergoing surgery already have risk-factors for VTE, including immobility, surgical wounds and systematic inflammation. The addition of SARS-CoV-2 infection may further increase this risk, but the extent and impact are unknown, and large scale, prospective patient-level data are lacking. Surgical patients may also carry asymptomatic SARS-CoV-2 infections, and whether this contributes to excess risk is also unknown.

Robust evidence is needed to enable clinicians and policymakers to minimise VTE risk in patients with SARS-CoV-2 infection. Ideally, such evidence would stratify the risk of VTE against both the duration of time between infection and surgery and presence or absence of symptoms. This study aimed to determine the VTE rate in patients with SARS-CoV-2 infection, stratified by current or prior infection.

Methods

This study was conducted according to guidelines set by the strengthening the reporting of observational studies in epidemiology (STROBE) statement for observational studies [11]. This was a planned sub-study and analysis from a prospective, international, multicentre cohort study of patients undergoing surgery during October 2020. Data were collected as part of this larger study in the same time frame. This prior study focused on overall 30-day mortality with specific reporting on pulmonary complications. The methods and findings of this study were published previously [12].

Hospitals providing surgery from any surgical specialty were eligible for participation. Study approvals for participating hospitals were secured in line with local and national regulations before entry into the study. Local investigators were required to confirm that all mandatory approvals were in place before data collection could begin. The study protocol was either registered as a clinical audit with institutional review or a research study obtaining ethical committee approval depending on local and national requirements. Informed patient consent was obtained if this was necessary to comply with local or national regulations. In the UK, this study was registered as a clinical audit in the central co-ordinating site and registered as either an audit or service evaluation at other recruiting institutions. Therefore, consent was not mandated from individual patients. Data were collected online and stored on a secure server running the Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, TN, USA) web application [13], based at the University of Birmingham, UK. Hospitals registered their interest to participate based on one or more surgical specialties. Participating specialties then collected data on consecutive patients who underwent surgery within their department during one or more pre-selected weeks between 5 October and 1 November 2020, with a 30-day postoperative follow-up period. No changes were made to local patient care protocols during the course of this study. Only anonymised, routine clinical data were collected.

Adult patients, aged 18 y and over, undergoing elective or emergency surgery for any indication, from any specialty, were eligible. As VTE events are very rare in patients aged <18 y, these patients were not included from this current analysis. Surgery was defined as any procedure routinely performed in an operating theatre by a surgeon. A list of excluded procedures can be found in online Supporting Information Table S1.

Baseline patient characteristics included age, ASA physical status and smoking status. Age was collected as a categorical variable in deciles of years and categorised into three groups for analysis: 18–49 y; 50–69 y; and ≥70 y. The ASA physical status was dichotomised to 1–2 or 3–5. Patients were identified as smokers if they were current smokers or had smoked in the six weeks before surgery. Data collected on pre-existing medical conditions included respiratory comorbidities (asthma; chronic obstructive pulmonary disease); congestive cardiac failure; cerebrovascular disease; chronic kidney disease; and ischaemic heart disease. Indications for surgery were classified as: benign disease; cancer; obstetrics; or trauma. Operative variables included urgency of surgery (elective or emergency); type of anaesthesia (local/regional or general); and grade of surgery (minor or major). National income was based on the World Bank's classification for each participating country [14].

A positive SARS-CoV-2 diagnosis was based on a patient having one or more of the following: a positive reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal swab; a positive rapid antigen test; chest computed tomography (CT) scan showing changes in keeping with locally implemented protocols that indicate SARS-CoV-2 infection; positive immunoglobulin G or immunoglobulin M antibody test; or clinical diagnosis of symptoms in keeping with COVID-19 in patients where no swab test or CT scan were available. Timing of diagnosis of

© 2021 The Authors. *Anaesthesia* published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists.

Table 1 Baseline patient, disease and operative characteristics stratified by SARS-CoV-2 status. Values are number (proportion).

	No SARS-CoV-2 n = 123,595	Peri-operative SARS-CoV-2 n = 2317	Recent SARS-CoV-2 n = 953	Previous SARS-CoV-2 n = 1148	p value
Age; y					
18–49	55,651 (45.0%)	968 (41.8%)	461 (48.4%)	480 (41.8%)	<0.001
50–69	41,633 (33.7%)	696 (30.0%)	332 (34.8%)	470 (40.9%)	
≥70	26,309 (21.3%)	653 (28.2%)	160 (16.8%)	198 (17.3%)	
Missing	2	0	0	0	
Sex					
Female	66,495 (53.8%)	1228 (53.0%)	493 (51.7%)	611 (53.2%)	0.506
Male	57,096 (46.2%)	1089 (47.0%)	460 (48.3%)	537 (46.8%)	
Missing	4	0	0	0	
ASA physical status					
1–2	91,229 (73.8%)	1399 (60.4%)	635 (66.6%)	759 (66.1%)	<0.001
3–5	32,323 (26.2%)	918 (39.6%)	318 (33.4%)	389 (33.9%)	
Missing	43	0	0	0	
Smoking					
No	103,387 (83.9%)	1949 (84.3%)	845 (88.9%)	1017 (88.8%)	<0.001
Yes	19,835 (16.1%)	364 (15.7%)	106 (11.1%)	128 (11.2%)	
Missing	373	4	2	3	
Respiratory comorbidity					
No	111,785 (90.5%)	2026 (87.5%)	854 (89.6%)	1027 (89.5%)	<0.001
Yes	11,713 (9.5%)	290 (12.5%)	99 (10.4%)	121 (10.5%)	
Missing	97	1	0	0	
Congestive heart failure					
No	118,829 (96.2%)	2151 (92.8%)	907 (95.2%)	1079 (94.0%)	<0.001
Yes	4738 (3.8%)	166 (7.2%)	46 (4.8%)	69 (6.0%)	
Missing	28	0	0	0	
Cerebral vascular disease					
No	119,253 (96.5%)	2190 (94.5%)	922 (96.7%)	1103 (96.1%)	<0.001
Yes	4314 (3.5%)	127 (5.5%)	31 (3.3%)	45 (3.9%)	
Missing	28	0	0	0	
Chronic kidney disease					
No	120,475 (97.5%)	2179 (94.0%)	900 (94.4%)	1094 (95.3%)	<0.001
Yes	3092 (2.5%)	138 (6.0%)	53 (5.6%)	54 (4.7%)	
Missing	28	0	0	0	
Ischaemic heart disease					
No	112,894 (91.4%)	1995 (86.1%)	856 (89.8%)	1037 (90.3%)	<0.001
Yes	10,673 (8.6%)	322 (13.9%)	97 (10.2%)	111 (9.7%)	
Missing	28	0	0	0	
Indication					
Benign disease	76,169 (61.6%)	1215 (52.4%)	561 (58.9%)	777 (67.7%)	<0.001
Malignancy	23,251 (18.8%)	421 (18.2%)	211 (22.1%)	231 (20.1%)	
Trauma	14,595 (11.8%)	436 (18.8%)	114 (12.0%)	91 (7.9%)	
Obstetric	9577 (7.8%)	245 (10.6%)	67 (7.0%)	49 (4.3%)	
Missing	3	0	0	0	

(continued)

© 2021 The Authors. *Anaesthesia* published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists.

Table 1 (*continued*)

	No SARS-CoV-2 n = 123,595	Peri-operative SARS-CoV-2 n = 2317	Recent SARS-CoV-2 n = 953	Previous SARS-CoV-2 n = 1148	p value
Grade of surgery					
Minor	47,178 (38.2%)	695 (30.0%)	285 (29.9%)	439 (38.2%)	<0.001
Major	76,392 (61.8%)	1622 (70.0%)	668 (70.1%)	709 (61.8%)	
Missing	25	0	0	0	
Urgency of surgery					
Elective	87,117 (70.5%)	965 (41.6%)	604 (63.4%)	857 (74.7%)	<0.001
Emergency	36,471 (29.5%)	1352 (58.4%)	349 (36.6%)	291 (25.3%)	
Missing	7	0	0	0	
Anaesthesia					
Local/regional	34,508 (27.9%)	707 (30.5%)	222 (23.3%)	285 (24.8%)	<0.001
General	89,035 (72.1%)	1609 (69.5%)	731 (76.7%)	863 (75.2%)	
Missing	52	1	0	0	
Country income					
High	20,624 (66.9%)	399 (55.3%)	242 (38.4%)	121 (58.8%)	<0.001
Upper middle	20,238 (16.4%)	636 (27.4%)	345 (36.2%)	352 (30.7%)	
Low middle/low	82,733 (16.7%)	1282 (17.2%)	366 (25.4%)	675 (10.5%)	
Missing	0	0	0	0	

SARS-CoV-2 in relation to the day of surgery was collected as a categorical variable and further collapsed into one of the following groups for analysis: no SARS-CoV-2; peri-operative SARS-CoV-2 (diagnosed 7 days before to 30 days after surgery); recent SARS-CoV-2 (diagnosed 1–6 weeks before surgery); or previous SARS-CoV-2 (diagnosed ≥7 weeks before surgery). Data were also collected on the presence or absence of respiratory or non-respiratory SARS-CoV-2 symptoms if patients had a pre-operative SARS-CoV-2 diagnosis. These were analysed as a combined group of patients with asymptomatic infection or those with previous symptoms now resolved, or patients with ongoing symptoms. Symptoms in patients with a postoperative SARS-CoV-2 diagnosis were not analysed as it was not possible to separate these from standard postoperative symptoms.

The primary outcome measure was VTE within 30 days following surgery. Venous thromboembolism was defined as either deep vein thrombosis (DVT) or pulmonary embolism (PE). Deep vein thrombosis was defined as lower limb DVT with or without symptoms that was proven radiologically; and PE was defined as symptomatic PE, radiologically proven or fatal PE discovered at post-mortem or as judged by the clinical team. Secondary outcome measures were postoperative pneumonia and mortality within 30 days of surgery. Full study definitions can be found in online Supporting Information Appendix S2.

Patients with data missing on VTE or SARS-CoV-2 status and patients aged <18 y were excluded in the analysis. The Chi-square test of independence was used to compare groups in terms of categorical data. For the primary outcome of VTE within 30 days of surgery, multivariable logistic regression analysis was used to evaluate the association of SARS-CoV-2 infection and VTE after surgery, which was summarised using OR (95%CI). The model included clinically relevant patient and operative factors in order to adjust for covariates and reduce the risk of confounding (baseline patient characteristics; pre-existing comorbidities; operative factors). Multivariable adjusted sub-group analyses were performed based on the main analysis to define the patients in which SARS-CoV-2 infection was associated with additional risk of postoperative VTE above the expected baseline risk of that sub-group. This was done in the following four sub-groups: major surgery; minor surgery; elective surgery; and emergency surgery. A multivariable adjusted analysis was also fitted for 30-day mortality as the outcome with VTE as the main explanatory variable, using clinically relevant patient and operative factors for adjustment. Analyses were performed with Stata SE version 16.1, (StataCorp, TX, USA).

Results

This analysis included 128,013 patients, from 1630 hospitals across 115 countries. Baseline patient and operative

© 2021 The Authors. *Anaesthesia* published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists.

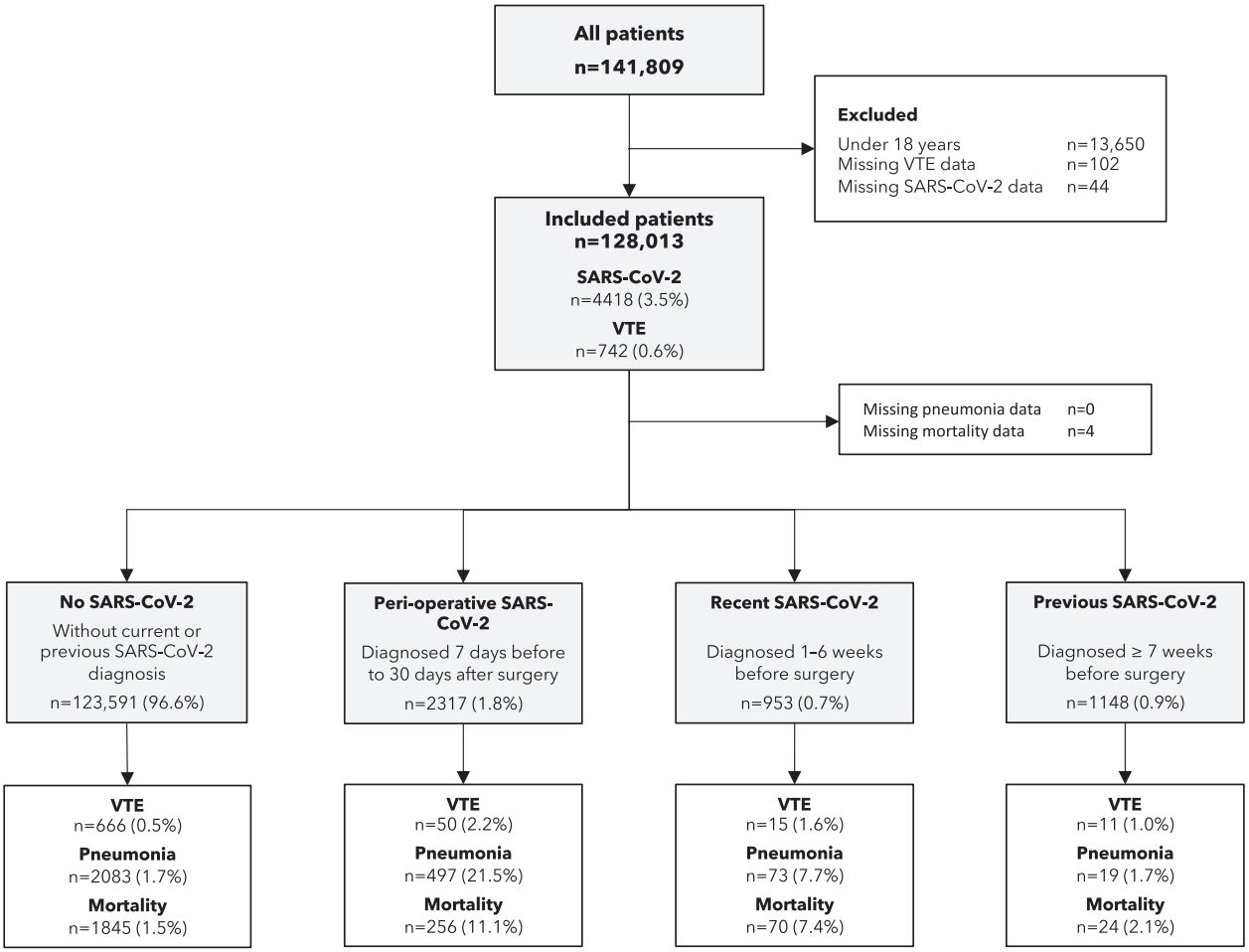

Figure 1 Flow diagram of patients showing venous thromboembolism (VTE), pneumonia, mortality and SARS-CoV-2 infection.

characteristics are shown in Table 1. Of these patients, 59,182 (46.2%) were men; 94,022 (73.5%) were ASA physical status 1–2 and 20,433 (16.0%) were smokers. The total number of patients who had a diagnosis of SARS-CoV-2 infection was 4418 (3.5%). The timing of SARS-CoV-2 diagnosis in relation to the day of surgery was peri-operative (7 days before to 30 days after surgery) for 2317 patients (1.8%); recent (1–6 weeks before surgery) for 953 patients (0.7%); and previous (≥7 weeks before surgery) for 1148 patients (0.9%; Fig. 1). Postoperative pneumonia was chosen as the best fitting variable to represent more severe SARS-CoV-2 infection. Proportionally, pneumonia occurred most frequently in patients with peri-operative SARS-CoV-2 (497 patients, 21.5%), followed by recent SARS-CoV-2 patients (73, 7.7%). Patients with previous SARS-CoV-2 (19, 1.7%) and no SARS-CoV-2 diagnosis (2083, 1.7%) had the same risk for postoperative pneumonia (Fig. 1). Compared with patients who did not have SARS-CoV-2 infection, patients with peri-operative SARS-CoV-2 were older (28.2% vs. 21.3%, $p < 0.001$), ASA physical status 3–5 (39.6% vs. 26.2%, $p < 0.001$), underwent emergency surgery more often (58.4% vs. 29.5%, $p < 0.001$) and had a greater comorbid burden (Table 1). This trend was also present when comparing patients without SARS-CoV-2 and those with recent and previous infection (Table 1).

Overall, the rate of postoperative VTE was 0.6% (742/128,013). Of these 742 patients, 44.3% (329) had a PE only, 47.5% (352) had a DVT only and 8.2% (61) had both. A full description of the VTE event rates in relation to patient and operative characteristics are reported in Table 2 and details of PE and DVT by specialty can be found in online Supporting Information Table S2. In adjusted analyses, significant predictors of postoperative VTE were peri-operative and recent SARS-CoV-2 infection; pneumonia; age >50 y; ASA physical status 3–5; chronic kidney disease; surgery for malignancy or trauma; major surgery; emergency surgery; having a general anaesthetic; and surgery performed in a country of upper-middle, low-

© 2021 The Authors. *Anaesthesia* published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists.

Table 2 Unadjusted venous thromboembolism (VTE) rates by patient, disease and operative factors. Values are number (proportion).

	No VTE n = 127,270	VTE n = 742	p value
Age; y			
18–49	57,368 (45.1%)	192 (25.9%)	<0.001
50–69	42,852 (33.7%)	279 (37.6%)	
≥70	27,049 (21.3%)	271 (36.5%)	
Missing	2	0	
Sex			
Female	68,447 (53.8%)	380 (51.2%)	0.161
Male	58,820 (46.2%)	362 (48.8%)	
Missing	4	0	
ASA physical status			
1–2	93,699 (73.7%)	323 (43.5%)	<0.001
3–5	33,529 (26.3%)	419 (56.5%)	
Missing	43	0	
Smoking			
No	106,582 (84.0%)	616 (83.2%)	0.578
Yes	20,309 (16.0%)	124 (16.8%)	
Missing	380	2	
Respiratory comorbidity			
No	115,067 (90.5%)	625 (84.2%)	<0.001
Yes	12,106 (9.5%)	117 (15.8%)	
Missing	98		
Congestive heart failure			
No	122,296 (96.1%)	670 (90.3%)	<0.001
Yes	4947 (3.9%)	72 (9.7%)	
Missing	28	0	
Cerebral vascular disease			
No	122,786 (96.5%)	682 (91.9%)	<0.001
Yes	4457 (3.5%)	60 (8.1%)	
Missing	28	0	
Chronic kidney disease			
No	123,962 (97.4%)	686 (92.5%)	<0.001
Yes	3281 (2.6%)	56 (7.5%)	
Missing	28	0	
Ischaemic heart disease			
No	116,174 (91.3%)	608 (81.9%)	< 0.001
Yes	11069 (8.7%)	134 (18.1%)	
Missing	28		
Indication			
Benign disease	78,373 (61.6%)	349 (47.0%)	<0.001
Malignancy	23,915 (18.8%)	199 (26.8%)	
Trauma	15,066 (11.8%)	170 (22.9%)	
Obstetric	9914 (7.8%)	24 (3.2%)	
Missing	3		
Grade of surgery			
Minor	48,465 (38.1%)	132 (17.8%)	<0.001
Major	78,781 (61.9%)	610 (82.2%)	
Missing	25		
Urgency of surgery			
Elective	89,192 (70.1%)	351 (47.3%)	<0.001
Emergency	38072 (29.9%)	391 (52.7%)	
Missing	7		
Anaesthesia			
Regional/local	35,597 (28.0%)	125 (16.8%)	<0.001
General	91,650 (72.0%)	617 (83.2%)	
Missing	53		
Country income			
High	84,572 (66.4%)	484 (65.2%)	0.268
Upper middle	21,453 (16.9%)	118 (15.9%)	
Low middle/low	21,246 (16.7%)	140 (18.9%)	
Missing	0		

middle or low income (Fig. 2, detailed in online Supporting Information Table S3). Pneumonia was strongly associated with postoperative VTE, and obstetric procedures had a lower rate of VTE when compared with benign (non-obstetric, non-cancer) surgery (Fig. 2).

When compared against the main adjusted analysis of all patients (Fig. 2), sub-group analysis of elective surgery patients only demonstrated a stronger association between peri-operative and recent SARS-CoV-2 infection and VTE; this effect was diminished in patients having emergency surgery (Fig. 3). Sub-group analysis in major surgery demonstrated similar risk of postoperative VTE to the main analysis in patients with peri-operative, recent or previous SARS-CoV-2 infection, although there was no significant effect in patients who had minor surgery (Fig. 3).

In patients with pre-operative SARS-CoV-2 infection, the presence of ongoing SARS-CoV-2 symptoms was associated with increased incidence of VTE when compared with patients without ongoing symptoms (Fig. 4). Ongoing symptoms were associated with an overall 4.6% (17/406) rate of postoperative VTE vs. 0.8% (21/2547) in patients who were asymptomatic or whose symptoms had resolved. This effect persisted even after stratifying patients by timing of SARS-CoV-2 diagnosis (Fig. 4) and was observed even in symptomatic patients with a SARS-CoV-2 diagnosis

© 2021 The Authors. *Anaesthesia* published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists.

≥7 weeks before surgery (5.7% in symptomatic patients vs. 0.7% in asymptomatic or resolved patients).

Overall, the rate of 30-day postoperative mortality was 1.7% (2195/128,009). When this was stratified by SARS-CoV-2 infection and postoperative VTE, unadjusted analyses demonstrated an incremental increase in mortality rates with SARS-CoV-2 infection and VTE (Table 3). In adjusted analyses, VTE was independently and strongly associated (OR 5.4 (95%CI 4.4–6.8)) with 30-day mortality (Table 4).

Discussion

This planned sub-study found that SARS-CoV-2 infection was independently associated with an increased incidence

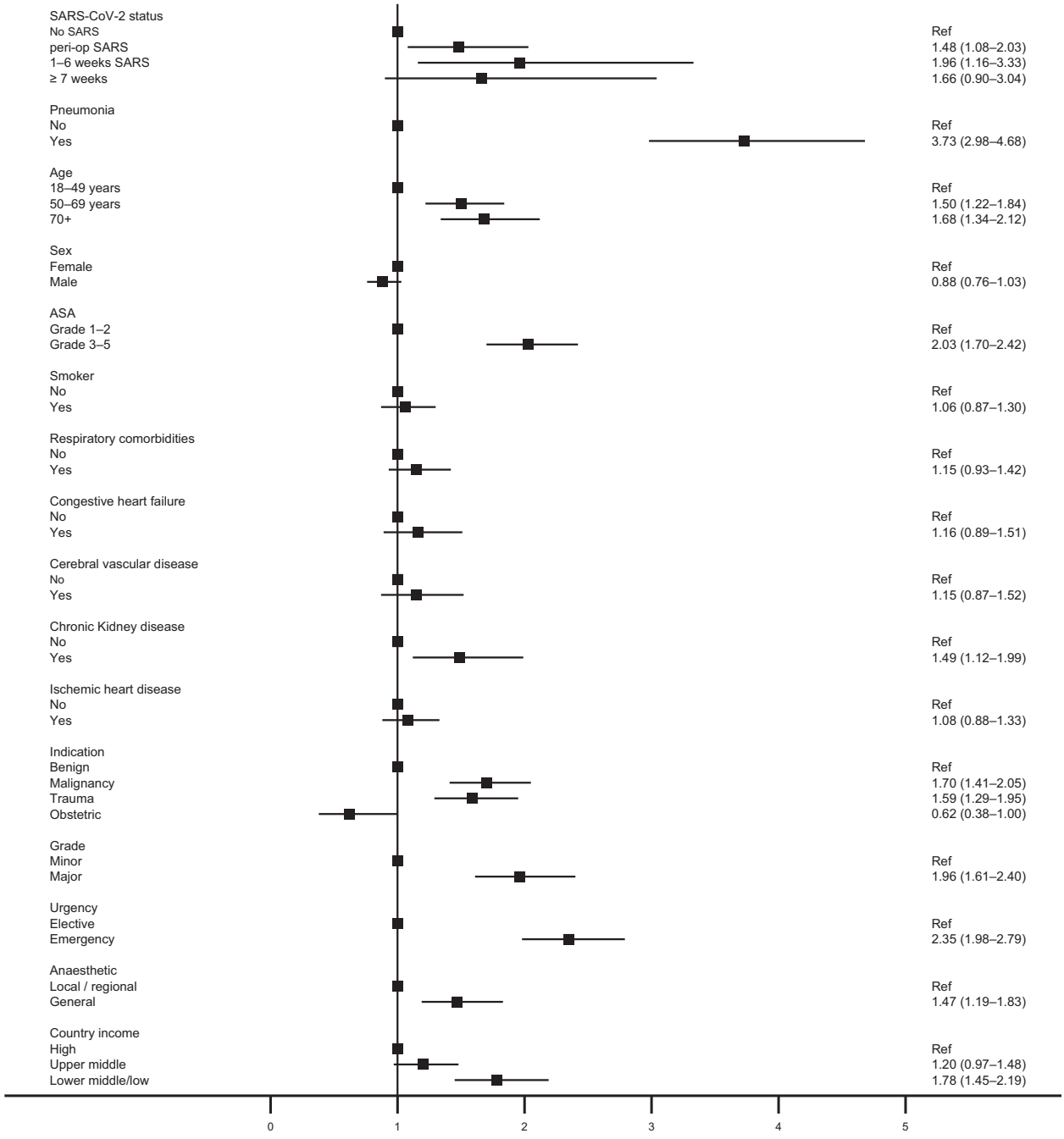

Figure 2 Forest plot of adjusted regression model for factors associated with venous thromboembolism. Figures show the reference value (Ref) and OR (95%CI) for the levels of each variable.

© 2021 The Authors. *Anaesthesia* published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists.

of postoperative VTE in patients with peri-operative and recent SARS-CoV-2 infection. In patients with pre-operative SARS-CoV-2, ongoing symptoms were associated with an increased rate of postoperative VTE, irrespective of how long before surgery the diagnosis was made. Pneumonia was strongly associated with postoperative VTE, possibly due to a combination of SARS-CoV-2-induced pneumonitis and a more difficult postoperative period involving infection, increased disease burden and greater immobility. Mortality was highest in patients with SARS-CoV-2 infection and VTE, and in adjusted analyses, SARS-CoV-2 and VTE were both independently associated with 30-day mortality. However, these results were limited by a lack of information on pre-operative anticoagulant use and postoperative VTE prophylactic regimens.

Overall, emergency surgery patients have a higher rate of postoperative VTE. However, sub-group analysis demonstrated that in elective patients, there was a greater additional VTE risk in patients with SARS-CoV-2 when compared with patients with no SARS-CoV-2. This additional risk was not as pronounced in emergency surgery patients. Without data on any differences in the VTE prophylaxis and anticoagulation regimes between the elective and emergency surgery patients, no firm conclusions can be drawn. However, it is possible that this could be a consequence of the greater number of VTE risk-factors associated with emergency surgery, resulting in any additional risk from SARS-CoV-2 infection having less of an impact on the overall risk of postoperative VTE. This translates into a disproportionately increased risk in patients

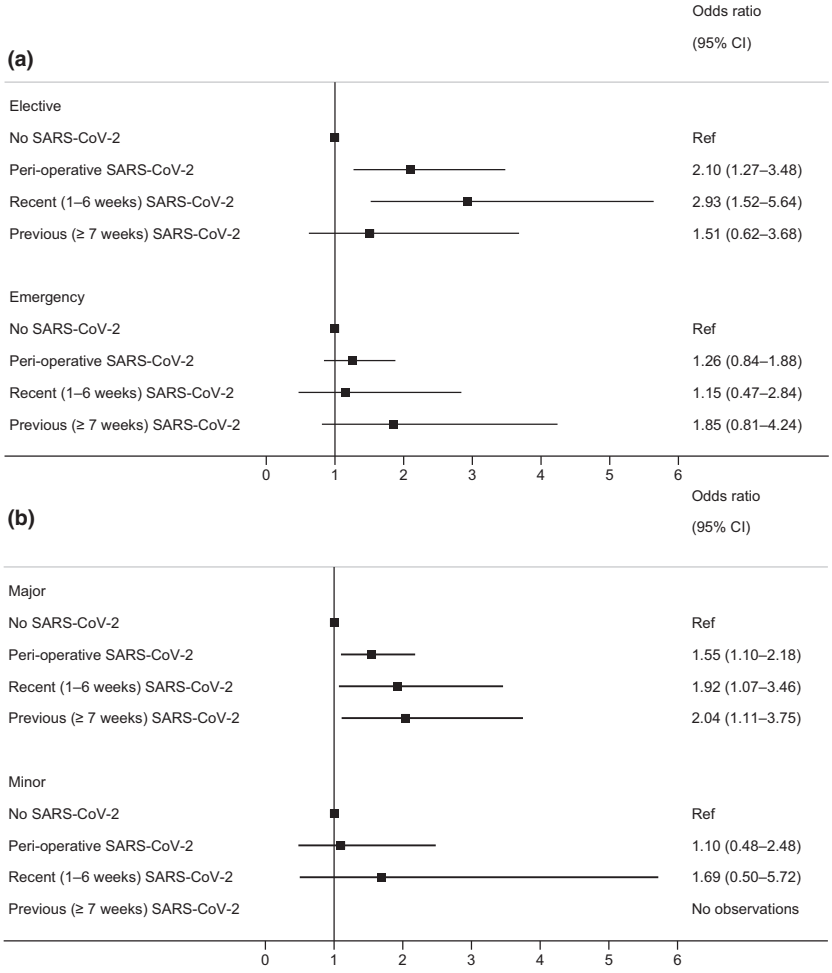

Figure 3 Adjusted sub-group analysis for venous thromboembolism in (A) elective and emergency patients and (B) major and minor surgery patients. Sub-group analyses are adjusted for the following variables: pneumonia; age; sex; ASA physical status; smoker; respiratory comorbidities; congestive heart failure; cerebral vascular disease; chronic kidney disease; ischaemic heart disease; indication; grade; urgency; anaesthesia; and country income. Full details can be found in online Supporting Information Tables S4 to S7. Figures show the reference value (Ref) and OR (95%CI) for the levels of each variable.

© 2021 The Authors. *Anaesthesia* published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists.

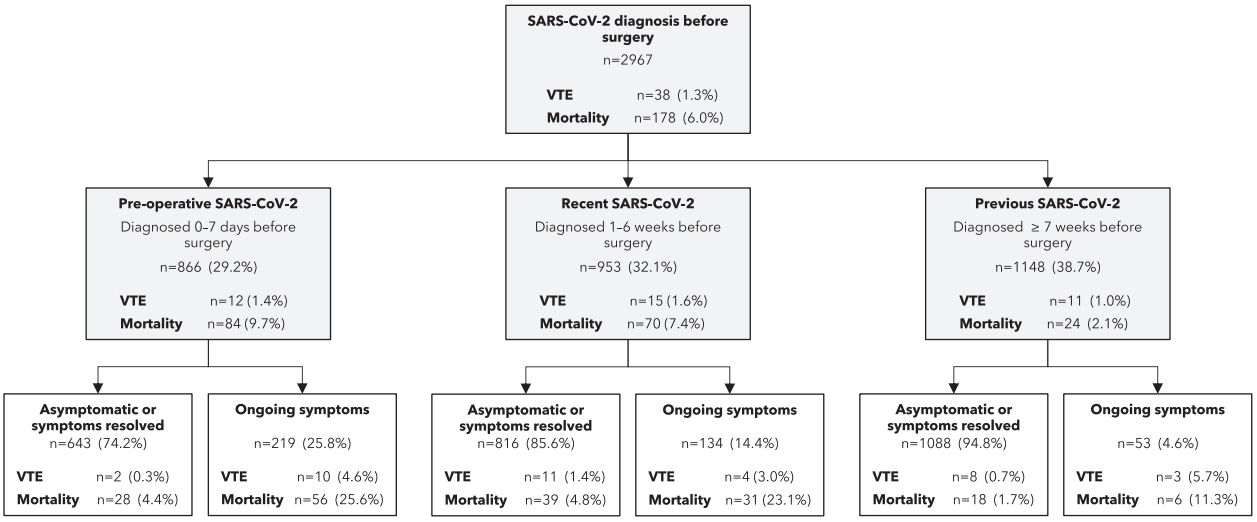

Figure 4 Venous thromboembolism (VTE) and 30-day mortality in patients with pre-operative SARS-CoV-2 by presence or absence of COVID-19 symptoms.

Table 3 Rate of 30-day mortality stratified by SARS-CoV-2 and venous thromboembolism (VTE) status. Values are fraction (proportion)

	No VTE		VTE		p value
All patients	2047/127,271	1.6%	148/742	20.0%	< 0.001
No SARS-CoV-2 infection	1728/122,929	1.4%	117/666	17.6%	< 0.001
Any SARS-CoV-2 infection	319/4342	7.4%	31/76	40.8%	< 0.001
Peri-operative SARS-CoV-2	236/2267	10.4%	20/50	40.0%	< 0.001
Recent SARS-CoV-2	60/938	6.4%	10/15	66.7%	< 0.001
Previous SARS-CoV-2	23/1137	2.0%	1/11	9.1%	0.103

undergoing elective surgery. Sub-group analysis also demonstrated greater additional risk in patients undergoing major surgery. This is most likely due to the smaller proportion of patients with peri-operative SARS-CoV-2 infection having minor elective surgery during the ongoing pandemic. Overall, minor surgery patients were exposed to fewer of the risk-factors for VTE, and baseline VTE rate was low. Concurrent SARS-CoV-2 infection was not associated with a significant increase in additional risk.

There have been numerous studies describing the elevated rates of VTE in medical patients who are hospitalised with COVID-19 on the ward or in the ICU, and results are pending for a number of ongoing randomised controlled trials investigating VTE prophylaxis and therapeutic protocols. To date, some studies describe increased bleeding risk with therapeutic (high) dosing of pharmacological VTE prophylaxis [10], and interim analyses of several randomised controlled trials report unfavourable outcomes with therapeutic pharmacological prophylaxis in patients with severe COVID-19 (i.e. admitted to ICU). However, improved outcomes and a reduced requirement for organ support has been seen in patients with moderate severity of COVID-19 (i.e. hospitalised) who receive therapeutic anticoagulation [15]. This highlights the challenge of anticoagulating patients with COVID-19, which is likely to be even more complex in patients having surgery, although our results suggest that anticoagulation in patients with previous, recent or peri-operative SARS-CoV-2 infection may be an important consideration.

Surgical patients represent a uniquely different cohort. Unlike medical patients, the primary reason for hospital admission for surgical patients is rarely due to COVID-19, and other co-existing primary pathology requiring surgical intervention is also present. Surgical patients undergo an operative procedure which artificially produces a wound that increases the risk of intra-operative and postoperative bleeding and sets in motion a cascade of inflammatory responses known to alter haemodynamics and coagulation. Paired with this, surgical patients often experience a period of reduced mobility immediately before, during and after

© 2021 The Authors. *Anaesthesia* published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists.

Table 4 Adjusted regression model for predictors for 30-day mortality. Values are fraction (proportion) or OR (95%CI)

	Mortality	OR (95%CI)	p value
VTE status			
No VTE	2047/127,267 (1.6%)		
VTE	594/742 (20.0%)	5.42 (4.36–6.75)	<0.001
SARS-CoV-2 status			
No SARS-CoV-2	1845/123,591 (1.5%)		
Peri-operative SARS-CoV-2	256/2317 (11.1%)	2.38 (2.00–2.82)	<0.001
Recent SARS-CoV-2	70/953 (7.4%)	2.78 (2.09–3.71)	<0.001
Previous SARS-CoV-2	24/1148 (2.1%)	1.13 (0.72–1.76)	0.597
Pneumonia			
No	1666/125,337 (1.3%)		
Yes	529/2672 (19.8%)	5.28 (4.65–6.00)	<0.001
Age; y			
18–49	429/57,557 (0.8%)		
50–69	757/43,130 (1.8%)	1.62 (1.41–1.86)	<0.001
≥70	1009/27,320 (3.7%)	2.67 (2.31–3.10)	<0.001
Sex			
Female	956/68,825 (1.4%)		
Male	1239/59,180 (2.1%)	1.06 (0.96–1.16)	0.269
ASA physical status			
1–2	543/94,020 (0.6%)		
3–5	1651/33,946 (4.9%)	4.32 (3.84–4.86)	<0.001
Smoking			
No	1796/105,399 (1.7%)		
Yes	387/20,045 (1.9%)	1.16 (1.02–1.32)	0.021
Respiratory comorbidities			
No	1843/115,688 (1.6%)		
Yes	349/12,223 (2.9%)	0.95 (0.83–1.08)	0.410
Congestive heart failure			
No	1859/122,962 (1.5%)		
Yes	336/5019 (6.7%)	1.54 (1.34–1.78)	< 0.001
Cerebral vascular disease			
No	1940/123,465 (1.6%)		
Yes	255/4516 (5.7%)	1.37 (1.18–1.60)	< 0.001
Chronic kidney disease			
No	1884/124,644 (1.5%)		
Yes	311/3337 (9.3%)	2.32 (2.00–2.69)	<0.001
Ischaemic heart disease			
No	1677/116,778 (1.4%)		
Yes	518/11,203 (4.6%)	1.01 (0.90–1.14)	0.842
Indication			
Benign	1174/78,720 (1.5%)		
Malignancy	569/24,112 (2.4%)	1.90 (1.68–2.14)	<0.001
Trauma	413/15,236 (2.7%)	0.91 (0.80–1.04)	0.160
Obstetric	39/9938 (0.4%)	0.39 (0.27–0.55)	<0.001

(continued)

© 2021 The Authors. *Anaesthesia* published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists.

Table 4 (*continued*)

	Mortality	OR (95%CI)	p value
Grade of surgery			
Minor	388/48,596 (0.8%)		
Major	1807/79,388 (2.3%)	1.80 (1.59–2.03)	<0.001
Urgency of surgery			
Elective	666/89,540 (0.7%)		
Emergency	1535/38,462 (4.0%)	5.62 (5.03–6.27)	<0.001
Anaesthetic			
Local/regional	306/35,721 (0.9%)		
General	1888/92,235 (2.1%)	1.90 (1.65–2.18)	<0.001
Country income			
High	1196/85,055 (1.4%)		
Upper middle	463/21,569 (2.2%)	2.43 (2.15–2.75)	<0.001
Lower middle/low	536/21,385 (2.5%)	4.73 (4.17–5.37)	<0.001

VTE, venous thromboembolism.
Peri-operative SARS-CoV-2, 7 days before to 30 days after surgery; recent SARS-CoV-2, 1–6 weeks before surgery; previous SARS-CoV-2, ≥ 7 weeks before surgery.

their operation, even for the young and normally fit and healthy. Furthermore, elective surgical patients are a group that can have a planned hospital admission, often following a period of self-isolation with reduced mobility, and many of these patients will have peri-operative mechanical ventilation. These differences in patient physiology and exposure signify a need to define VTE risk specifically in surgical patients, not only to provide a baseline understanding of peri-operative risk in the setting of COVID-19, but also to work towards constructing future VTE regimens specifically suited to surgical patients with active or prior SARS-CoV-2 infection.

This study has several limitations. First, information on postoperative VTE prophylaxis regimens (mechanical and pharmacological) and pre-existing anticoagulation for specific patient comorbidities associated with prophylaxis (e.g. atrial fibrillation) were not collected as part of this study. During the period of study (October 2020), patients with known SARS-CoV-2 infection might have already empirically received enhanced VTE prophylaxis based on earlier reports associating COVID-19 and an increased risk of VTE. The present study data report outcomes from VTE care and prophylaxis which were deemed acceptable and appropriate for each individual patient in participating departments from each country at the time of the study. Any additional risk could be interpreted as risk above prevailing VTE protocols and practice. Second, this study did not include patients who had an asymptomatic VTE diagnosed as a result of screening. Though there are reports of VTE screening being carried out in high-risk patient groups, the clinical relevance of asymptomatic, distal DVT is uncertain and could lead to overdiagnosis and skewed results [1]. Venous thromboembolism diagnoses made in this study were likely due to symptomatic presentation or a high index of clinical suspicion leading to radiological confirmation, and we believe that the incidence of VTE in this study is representative of the true, clinically relevant figure. Third, the rate of SARS-CoV-2 infection in October of 2020 and the overall incidence of VTE in surgical patients were both relatively low. Despite the large number of patients in this study, some sub-group analyses have resulted in small patient samples, and these should be interpreted with caution. Finally, there exists the possibility that some patients who had SARS-CoV-2 infection never attained a formal diagnosis and were therefore classified as no SARS-CoV-2. This most likely occurred in patients with asymptomatic infection. This study reported a high proportion of patients with asymptomatic infection which provides some reassurance that these cases were appropriately counted. While asymptomatic patients could have been misclassified as no SARS-CoV-2, this misclassification would have resulted in an underestimation of the overall difference in VTE between groups, and our estimate could be considered conservative.

Despite this study's limitations, recent and peri-operative SARS-CoV-2 infection may be an independent risk-factor for postoperative VTE, and increased awareness and surveillance should be considered. At a minimum, we suggest close adherence to routine standard VTE prophylaxis for surgical patients, including the use of

© 2021 The Authors. *Anaesthesia* published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists.

pharmacological agents when bleeding risk is minimal, and increased vigilance with a heightened index of suspicion and a lower threshold for definitive diagnostic testing in patients presenting with signs of VTE. Routine postoperative care of surgical patients should include interventions to reduce VTE risk in general, and further research is needed to define the optimal protocols for VTE prophylaxis and treatment for surgical patients in the setting of SARS-CoV-2 infection.

Acknowledgements

This study was registered prospectively at clinicaltrials.gov (NCT04509986). Funding was provided by: National Institute for Health Research (NIHR) Global Health Research Unit; Association of Coloproctology of Great Britain and Ireland; Bowel and Cancer Research; Bowel Disease Research Foundation; Association of Upper Gastrointestinal Surgeons; British Association of Surgical Oncology; British Gynaecological Cancer Society; European Society of Coloproctology; Medtronic; NIHR Academy; Sarcoma UK; The Urology Foundation; Vascular Society for Great Britain and Ireland; and Yorkshire Cancer Research. The views expressed are those of the authors and not necessarily those of the funding partners. No other competing interests declared.

References

1. 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. *Thrombosis Journal* 2021; **19**: 15.
2. 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. *Research and Practice in Thrombosis and Haemostasis* 2020; **4**: 1178–91.
3. Al-Ani F, Chehade S, Lazo-Langner A. Thrombosis risk associated with COVID-19 infection. A scoping review. *Thrombosis Research* 2020; **192**: 152–60.
4. Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AW, Di Nisio M. Venous thromboembolism in patients with COVID-19: systematic review and meta-analysis. *Thrombosis Research* 2020; **196**: 67–74.
5. Potere N, Valeriani E, Candeloro M, et al. Acute complications and mortality in hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. *Critical Care* 2020; **24**: 389.
6. 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.
7. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and Standardization Committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *Journal of Thrombosis and Haemostasis* 2020; **18**: 1859–65.
8. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing COVID-19. [NG191]. 23 March 2021, last updated 08 April 2021. https://www.nice.org.uk/guidance/ng191 (accessed 24/05/2021).
9. Conti CB, Henchi S, Coppeta GP, Testa S, Grassia R. Bleeding in COVID-19 severe pneumonia: the other side of abnormal coagulation pattern? *European Journal of Internal Medicine* 2020; **77**: 147–9.
10. Leentjens J, van Haaps TF, Wessels PF, Schutgens REG, Middeldorp S. COVID-19-associated coagulopathy and antithrombotic agents-lessons after 1 year. *Lancet Haematology* 2021; **8**: e524–33.
11. Ev E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *British Medical Journal* 2007; **335**: 806–8.
12. Collaborative C, Collaborative G. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. *Anaesthesia* 2021; **76**: 748–58.
13. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics* 2009; **42**: 377–81.
14. World Bank. World Bank Country and Lending Groups. 2021. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups (accessed 24/03/2021).
15. ATTACC Investigators. ACTIV-4a & REMAP-CAP multiplatform RCT - Results of interim analysis. 2021. https://www.attacc.org/presentations (accessed 24/03/2021).

Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. COVIDSurg Collaborative authors (all PubMed indexed co-authors).

Appendix S2. Definitions of terms used in this study.

Tables S1. List of excluded procedures.

Tables S2. Ranked VTE rates alongside PE and DVT rates by specialty in all patients of any SARS-CoV-2 status

Tables S3. Adjusted regression model for factors associated with venous thromboembolism (shown in Figure 3).

Tables S4. Adjusted sub-group analysis for VTE in elective patients only.

Tables S5. Adjusted sub-group analysis for VTE in emergency patients only.

Tables S6. Adjusted sub-group analysis for VTE in major surgery patients only.

Tables S7. Adjusted sub-group analysis for VTE in minor surgery patients only.

© 2021 The Authors. *Anaesthesia* published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists.