Full Length Article

Venous thromboembolism in patients hospitalised with COVID-19 in England

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ABSTRACT

Background: The aim of this study was to detail the incidence of venous thromboembolism (VTE) in patients hospitalised with COVID-19 in England.
Methods: This was an exploratory retrospective analysis of observational data from the Hospital Episode Statistics dataset for England. All patients aged ≥18 years in England with a diagnosis of COVID-19 who had a hospital stay that was completed between 1st March 2020 and 31st March 2021 were included. A recorded diagnosis of VTE during the index stay or during a subsequent admission in the six weeks following discharge was the primary outcome in the main analysis. In secondary analysis, VTE diagnosis was the primary exposure and in-hospital mortality the primary outcome.
Results: Over the 13 months, 374,244 unique patients had a diagnosis of COVID-19 during a hospital stay, of whom 17,346 (4.6%) had a recorded diagnosis of VTE. VTE was more commonly recorded in patients aged 40–79 years, males and in patients of Black ethnicity, even after adjusting for covariates. Recorded VTE diagnosis was associated with longer hospital stay and higher adjusted in-hospital mortality (odds ratio 1.35 (95% confidence interval 1.29 to 1.41)).
Conclusions: VTE was a common complication of hospitalisation with COVID-19 in England. VTE was associated with both increased length of stay and mortality rate.

1. Introduction

When patients are hospitalised with COVID-19, this is often for treatment of symptoms of acute respiratory distress. However, the sequalae of COVID-19 are wide ranging, with cardiovascular, renal and gastrointestinal symptoms common [1]. Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is often reported in patients hospitalised with COVID-19 [2,3]. Given that hospitalisation with acute medical illness is a major risk factor for VTE, the association with COVID-19 is unsurprising. However, reports of increased rates of VTE occurring in patients hospitalised with COVID-19 despite use of thromboprophylaxis [4,5], along with laboratory evidence of hypercoagulability [6], highlight COVID-19 infection as highly prothrombotic.

Reports on the incidence of VTE in patients hospitalised with COVID-19 are often on relatively small groups of patients at single sites. As such, reported incidence varies widely, depending on the exact setting. In a systematic review by Jimenez et al. [2], the pooled incidence of VTE was 17.0%, but within individual studies rates varied from 0 to 85.4%. The smallest study included only 10 patients and the largest 3404 patients. The authors also note the limited data on the association between VTE and mortality in COVID-19 patients.

The aim of this study was to use an administrative database of all patients hospitalised with COVID-19 in the National Health Service (NHS) in England to explore the characteristics of patients with a diagnosis of VTE and to report outcomes for these patients.

2. Methods

2.1. Ethics

Consent from individuals involved in this study was not required. The analysis and presentation of data follows current NHS Digital guidance for the use of Hospital Episodes Statistics (HES) data for research purposes and is anonymised to the level required by ISB1523 Anonymisation Standard for Publishing Health and Social Care Data [7].

2.2. Study design and data collection

This was a retrospective exploratory analysis of HES data. HES data are collected for all NHS-funded patients admitted to hospitals in England. The data are entered by individual NHS hospital trusts throughout England and are curated by NHS Digital. Data are entered by trained clinical coders and data collection is mandatory for each trust.

2.3. Timing, case ascertainment, inclusion and exclusion criteria

We reviewed HES data for all completed episodes of hospital care in England with a discharge date from 1st March 2020 to 31st March 2021 that involved a diagnosis of COVID-19. The time period was designed to cover the first and second waves of COVID-19 in England, but largely avoids the impact of vaccinations. Vaccination started in England on 8th December 2020, with a relatively slow early roll-out to the elderly, clinically vulnerable and healthcare workers.

We only considered completed episodes of care, where the patient had been discharged and their outcome was known (either discharged alive or having died during their stay). Patients aged <18 years were excluded. Cases of COVID-19 were identified using the International Statistical Classification of Disease and Related Health Problems 10th edition (ICD-10) codes U07.1 and U07.2. U07.1 is assigned where the presence of COVID-19 has been confirmed by laboratory testing. U07.2 is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available.

Where a patient had multiple admissions during the study period, only the chronologically first admission was retained for the main analysis. This ensured that all admissions were independent of one another at a patient level. The data extraction process is summarised in Fig. 1. These criteria defined the sample size.

3. Primary exposure and outcome

Diagnosis of venous thromboembolism (VTE) was the primary outcome of interest in the main analysis but also treated as an exposure variable in secondary analysis. VTE was identified as present if any of the ICD-10 codes listed in Supplementary material Table S1 were present in any position in the diagnostic record during the index stay or on a subsequent hospital admission within 42 days (six weeks) of discharge. The HES database was searched for non-COVID-19 hospital admissions for the selected patients in the four years before the index admission. If VTE had been recorded in any such prior admission without COVID-19 being recorded for that admission, then it was assumed that the VTE was pre-existing and the patient was not considered to have VTE associated with COVID-19.

Where data are presented for those diagnosed with VTE during the index stay and those during a subsequent admission, if a diagnosis of VTE was recorded on both admissions it was only retained for the index admission.

Within patients with a VTE diagnosis, PE was identified where the ICD-10 codes I26.0 or I26.9 were present.

4. Outcome

In secondary analysis, the primary outcome was in-hospital mortality
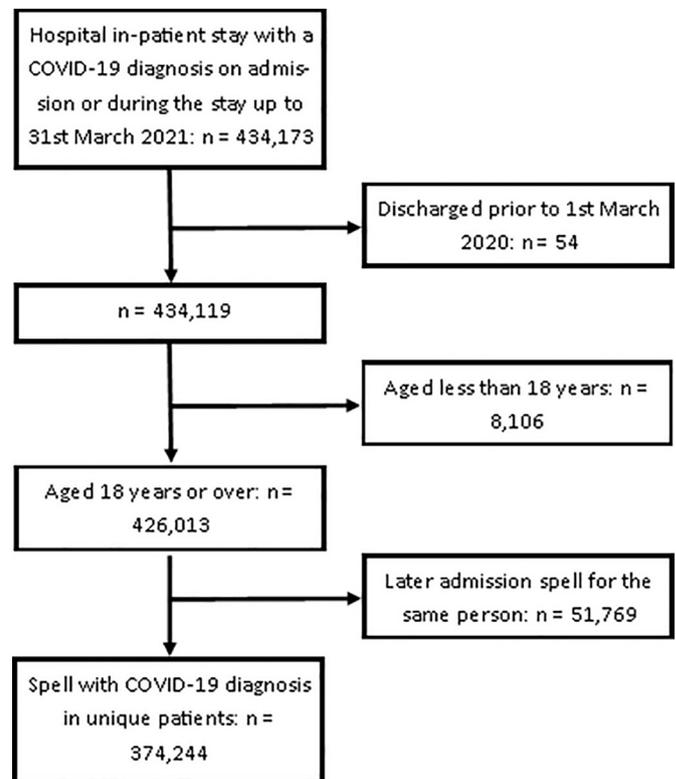
Fig. 1. Data extraction process.

as recorded by the Office for National Statistics (ONS). An in-hospital death was recorded if the date of death was the same as or ± one day of the date of hospital discharge recorded in HES. A secondary outcome was length of stay.

5. Covariates

Age: Categorised as 18–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years and ≥80 years. The categorisation was chosen to reflect that used in previous studies [8–12].

Sex: Male or female.

Ethnicity: Coded in categories used by NHS Digital (White, South Asian, Other Asian, Black, Mixed, Other).

Deprivation: Recorded using the Index of Multiple Deprivation (IMD) for the Lower Super Output Area (LSOA) of the patients' home address, with scores categorised into quintiles based on national averages.

Comorbidities: These were the 14 comorbidities used to construct the Charlson Comorbidity Index (peripheral vascular disease, congestive heart failure, acute myocardial infarction, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease/rheumatic disease, peptic ulcer, liver disease (mild and moderate/severe), diabetes (with and without chronic complications), paraplegia/hemiplegia, renal disease, cancer (primary and metastatic), HIV/AIDS) [13]. The comorbidity was deemed present if it was recorded in HES as a secondary diagnosis in the index admission or as a primary or secondary diagnosis in any admission during the previous year, in accordance with the recommendations of Quan et al [14].

Obesity: Recorded as present if the ICD-10 code E66 was used as a diagnostic code during the admission.

Critical care admission: Patients who had an admission to critical care (high dependency unit or intensive care unit).

6. Data management and statistical analyses

Analysis used standard statistical software: Microsoft Excel

(Microsoft Corp, Redmond, WA, USA), Stata (StataCorp LLC, College Station, TX, USA) and Alteryx (Alteryx Inc., Irvine, CA, USA). All data are described by frequency and percentage. When presenting data by month of admission, March 2021 is not included as patients admitted in this month would have to have been discharged by the end of the month to be included in the dataset, creating a bias towards patients with shorter hospital stay.

Hierarchical multi-level logistic regression models were developed using the 'melogit' command in Stata. In the primary analysis, the association between VTE diagnosis and the covariates listed above was investigated. In secondary analysis the association between the outcome in-hospital mortality and VTE (treated as the exposure variable) after adjusting for all listed covariates was investigated. Two-level intercept only models were constructed, allowing adjustment for clustering of patients within hospital trusts, with hospital trust as the random effect. The covariates listed above were included as fixed effects in the models. All covariates were modelled as described. Due to differential rates of access to critical care based on clinical presentation and/or an agreed ceiling of care, critical care was not included in the main regression model but added as an additional variable to assess its association with VTE.

7. Sensitivity analysis

We repeated the modelling using data for patients with a stay of ≥ 4 days. This was to assess whether the lower rates of diagnosis of VTE in patients aged ≥ 70 years was due to a disproportionate number of early deaths in older patients before a diagnosis of VTE could be made. We also repeated the modelling only considering VTE diagnosed during the index spell. This was done to assess any effect of bias in patients who survived to discharge.

8. Missing data

Only for sex (0.01%), deprivation (2.2%) and ethnicity (6.4%) were there missing data (see Table 1). For ethnicity, a number of patients did not state their ethnicity, although an answer was recorded for all patients. In these cases, HES was searched for the most recent hospital admission for the same patient where ethnicity had been recorded and this value was used. No attempt was made to impute missing values, meaning that model outputs are based only on complete records. The model outputs should be interpreted, within the context of exploratory analysis, as mutually adjusted associations rather than as causal relationships [15].

9. Results

Data were available for 374,244 patients admitted to 188 hospital trusts in England. Of these, 17,346 (4.6%) had a diagnosis of VTE, with 13,525 (78.0%) recorded during the index admission and 3821 (22.0%) during the 42 day follow-up period. Pulmonary embolism was present in 14,919 (86.0%) of VTE cases. There were 84,491 (22.6%) in-hospital deaths during the index admission, with 3409 (25.2%) deaths in those with VTE during the index admission and 81,082 (22.5%) deaths in those without VTE during the index admission.

For patients who survived to hospital discharge from the index spell ($n = 289,753$), the rate of post-discharge VTE within 42 days was 1.3%. Of the 34,239 (9.1%) patients admitted to critical care during their stay, 3678 (10.7%) had a diagnosis of VTE, compared to 13,668 (4.0%) diagnoses of VTE in the 340,005 patients not admitted to critical care.

For those admitted to critical care the median length of stay for those with VTE was 19 days (IQR 10 to 34) and for those without VTE was 14 days (IQR 8 to 25). For those not admitted to critical care the median length of stay for those with VTE was 9 days (IQR 4 to 19) and for those without VTE was 7 days (IQR 3 to 15).

The demographic and comorbidity profile for all patients and only

Table 1

Demographic and comorbidity profile of included patients and those with a recorded diagnosis of venous thromboembolism during the index admission or a readmission within 42 days.

Variable	Number of patients ($n = 374,244$)	Number of patients with venous thromboembolism ($n = 17,346$)
Age band (years)		
18–39	36,206	989 (2.7%)
40–49	30,973	1560 (5.0%)
50–59	51,436	3156 (6.1%)
60–69	58,433	3787 (6.5%)
70–79	77,172	3935 (5.1%)
≥ 80	120,024	3919 (3.3%)
Sex (missing = 46)		
Female	175,607	6907 (3.9%)
Male	198,591	10,435 (5.3%)
Deprivation quintile (missing = 8072)		
1 (most deprived)	97,379	4405 (4.5%)
2	81,611	3870 (4.7%)
3	69,640	3075 (4.4%)
4	62,729	2989 (4.8%)
5 (least deprived)	54,813	2592 (4.7%)
Ethnicity (missing = 24,072)		
White	282,442	12,523 (4.4%)
Black	3678	1089 (6.6%)
South Asian	11,214	1007 (3.8%)
Other Asian	11,516	378 (4.5%)
Mixed	3373	170 (5.0%)
Other	11,889	723 (5.5%)
Comorbidity		
Peripheral vascular disease	19,273	878 (4.6%)
Chronic heart failure	50,587	1882 (3.7%)
Acute myocardial infarction	33,602	1125 (3.3%)
Cerebrovascular disease	34,856	1433 (4.1%)
Dementia	46,997	1255 (2.7%)
Pulmonary disease	96,492	4440 (4.6%)
Connective tissue disease	11,810	518 (4.4%)
Peptic ulcer	2796	194 (6.9%)
Diabetes without chronic complications	89,252	3742 (4.2%)
Diabetes with chronic complications	11,060	348 (3.1%)
Hemiplegia/paraplegia	8308	370 (4.5%)
Renal disease	66,930	2244 (3.4%)
Primary cancer	19,533	920 (4.7%)
Metastatic carcinoma	11,450	831 (7.3%)
Mild liver disease	13,780	828 (6.0%)
Moderate/severe liver disease	4039	140 (3.5%)
HIV/AIDS	458	27 (5.9%)
Obesity	40,907	2295 (5.6%)

Percentages refer to the proportion of patients with a diagnosis of venous thromboembolism relative to all patients in that group.

for those with VTE is shown in Table 1. The proportion of patients with VTE increased with age up to the 60–69 years age groups and was less common in older age groups. It was more common in males and in patients of Black ethnicity. In general, VTE was less common in patients with age-related comorbidities, such as dementia, chronic heart failure, acute myocardial infarction and cerebrovascular disease. It was more common in patients with peptic ulcer, mild liver disease, metastatic carcinoma, HIV/AIDS and obesity. Supplementary material Table S2 summarises the profile of patients with VTE categorised into those with VTE during the index admission and those with VTE diagnosed during a readmission within 42 days. The demographic and co-morbidity profile of the two groups was similar.

The median age of all patients was 71 years (IQR 55 to 82) but was notably lower for patients with mild liver disease (64 years: IQR 53 to

75), HIV/AIDS (54 years: IQR 47 to 61) and obesity (60 years: IQR 48 to 71) and notably higher for patients with peptic ulcer (76 years: IQR 65 to 84) and metastatic carcinoma (74 years: IQR 64 to 81). There was evidence of a modest trend towards increased rates of VTE diagnoses over time (see Fig. 2).

Table 2 summarises the output of multivariable multilevel logistic regression models of factors associated with VTE diagnosis for all patients, for those admitted to critical care and for those who survived to discharge and had VTE diagnosed during a subsequent admission. For all patients, those aged 60–69 years had the greatest odds of VTE. VTE diagnosis was also strongly associated with male sex, Black ethnicity and the comorbidities peptic ulcer, mild liver disease, metastatic carcinoma and obesity. The pattern of odds ratios when considering only VTE diagnosed on readmission in patients who survived the index admission was very similar. For critical care patients the pattern was also similar, but with a weaker association with age and with higher odds of VTE with cerebrovascular disease and lower odds of VTE with metastatic carcinoma and obesity.

Crude in-hospital mortality rates for those with VTE during the index spell and those without across demographic and comorbidity groups are presented in Table 3. The higher mortality rate in those with VTE, compared to those without VTE, was most striking in younger patients. In patients aged <70 years, 7.4% of all in-hospital deaths recorded VTE as a diagnosis, compared to 3.2% of all deaths in patients aged ≥70 years. Despite having a relatively low risk of being diagnosed with VTE, Asian ethnicity patients had a higher mortality rate if diagnosed with VTE. Mortality rates were generally similar or slightly higher for patients with VTE than without across all comorbidity groups, although the difference was more obvious for patients with diabetes with complications, moderate/severe liver disease and HIV/AIDS. After adjusting for covariates through multivariable multilevel logistic regression modelling VTE was associated with greater odds of in-hospital mortality (OR 1.35 (95% CI 1.29 to 1.41)). The association was slightly attenuated when considering only the sub-set of patients admitted to critical care (OR 1.17 (85% CI 1.06 to 1.28)).

VTE was much less commonly diagnosed during the index admission in those with an index length of stay <4 days: 2096 VTE diagnoses in 104,263 patients (2.0%), compared to patients with length of stay ≥4 days: 11,429 VTE diagnoses in 269,981 patients (4.2%). The results of the sensitivity analysis for covariates associated with VTE diagnosis in those with a length of stay ≥4 days and when only considering index diagnoses of VTE are presented in Supplementary material Table S3 and are similar to the main analysis. The association between in-hospital

mortality and VTE was similar as when considering all patients, OR (1.33 (95% CI 1.27 to 1.40)) in this reduced dataset.

10. Discussion

To our knowledge this is the largest study to date to look at the incidence of VTE in COVID-19 patients [2]. VTE was more commonly recorded in patients aged 40–79 years, in males, for Black ethnicities, in people with pre-existing peptic ulcer and metastatic carcinoma, even after adjusting for covariates. Given metastatic cancer [16,17], male sex [18] and Black ethnicity [19], are all well recognised risk factors for VTE these associations are as expected [20]. These associations may contribute to reported higher mortality rates in these groups [9,21]. For patients with peptic ulcer, higher VTE rates could be related to bleeding and consequent lack of anticoagulant thromboprophylaxis [22–24]. The vast majority of VTE reported were PE. This is consistent with previous studies from relatively large (>100 VTE patients) prospective studies [4,5,25].

It is well established that rates of VTE increase with age [18,20]. It is therefore surprising that VTE was less common in those aged 70 years and over than in some younger age groups. It is likely that there will be some degree of under-recording of VTE in older patients and this may account for this observation. Older patients, particularly those who are most acutely ill, may be less likely to be investigated for VTE as other aspects of care are prioritised. Likewise, patients who die soon after admission to hospital may be too unstable to proceed with diagnostic imaging. To try to overcome this potential cofounder we analysed patients who stayed for four days or more separately. However, a similar fall off in the proportion of patients diagnosed with VTE in older age groups was still evident. Therefore, some degree of under-recording of VTE in older patients seems likely. Whether this is due to VTE investigations not being carried out or identified VTE not being record in medical notes is not clear.

In a systematic review by Jimenez et al. [2] of data for 18,093 patients across 47 studies, the pooled incidence of VTE was 17.0% (95% CI, 13.4% to 20.9%). However, estimates varied widely depending on the study design: 33.1% by screening versus 9.8% by clinical diagnosis, 27.9% in a critical care unit versus 7.1% on the ward, 25.5% in prospective studies versus 12.4% in retrospective studies. The largest study included 1477 patients. Although our estimate of the incidence of VTE was lower than these values, at 4.9%, this may be partly explained by the fact our study is retrospective and based on clinical coding from medical notes. We will not have identified VTE cases which would have been
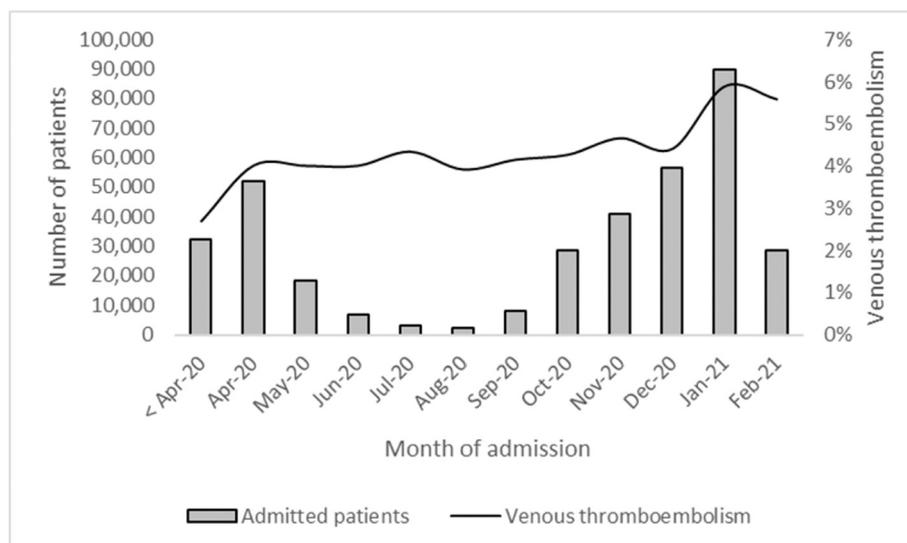
Fig. 2. Number of patients and proportion with venous thromboembolism per month of admission.

Table 2
Summary of multivariable multilevel logistic regression models of factors associated with venous thromboembolism.

Variable	All patients (n = 374,244)	Patients admitted to critical care (n = 34,239)	In survivors on readmission (n = 289,753)
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Age band (years)			
18–39	1 (reference)	1 (reference)	1 (reference)
40–49	1.83 (1.68 to 2.00)	1.44 (1.20 to 1.72)	1.53 (1.29 to 1.82)
50–59	2.30 (2.13 to 2.49)	1.53 (1.30 to 1.80)	1.95 (1.67 to 2.28)
60–69	2.53 (2.34 to 2.74)	1.66 (1.41 to 1.96)	2.13 (1.82 to 2.48)
70–79	2.18 (2.02 to 2.36)	1.26 (1.06 to 1.50)	2.24 (1.92 to 2.62)
≥80	1.56 (1.43 to 1.69)	0.79 (0.61 to 1.01)	1.91 (1.63 to 2.24)
Sex			
Female	1 (reference)	1 (reference)	1 (reference)
Male	1.27 (1.23 to 1.32)	1.25 (1.15 to 1.35)	1.31 (1.22 to 1.40)
Deprivation quintile			
1 (most deprived)	1 (reference)	1 (reference)	1 (reference)
2	1.05 (1.00 to 1.10)	1.04 (0.94 to 1.16)	1.03 (0.93 to 1.14)
3	1.00 (0.95 to 1.05)	0.97 (0.87 to 1.09)	1.04 (0.94 to 1.15)
4	1.09 (1.03 to 1.15)	1.07 (0.95 to 1.21)	1.11 (0.99 to 1.23)
5 (least deprived)	1.06 (1.00 to 1.12)	1.03 (0.91 to 1.18)	1.07 (0.95 to 1.20)
Ethnicity			
White	1 (reference)	1 (reference)	1 (reference)
Black	1.35 (1.26 to 1.45)	1.35 (1.17 to 1.56)	1.08 (0.92 to 1.27)
South Asian	0.87 (0.81 to 0.94)	1.10 (0.97 to 1.25)	0.95 (0.83 to 1.10)
Other Asian	0.90 (0.81 to 1.01)	1.15 (0.96 to 1.38)	1.08 (0.88 to 1.34)
Mixed	1.06 (0.90 to 1.25)	0.94 (0.68 to 1.30)	1.07 (0.77 to 1.48)
Other	1.04 (0.96 to 1.13)	1.16 (0.99 to 1.35)	1.01 (0.85 to 1.20)
Comorbidities[a]			
Peripheral vascular disease	1.05 (0.98 to 1.13)	1.02 (0.86 to 1.22)	0.97 (0.83 to 1.14)
Congestive heart failure	0.91 (0.87 to 0.97)	1.09 (0.96 to 1.24)	0.93 (0.82 to 1.04)
Acute myocardial infarction	0.74 (0.69 to 0.79)	0.68 (0.59 to 0.80)	0.85 (0.74 to 0.96)
Cerebrovascular disease	0.98 (0.92 to 1.04)	1.53 (1.32 to 1.77)	0.96 (0.84 to 1.10)
Dementia	0.65 (0.61 to 0.70)	0.57 (0.32 to 1.00)	0.75 (0.66 to 0.86)
Chronic pulmonary disease	1.00 (0.97 to 1.04)	0.98 (0.90 to 1.07)	1.20 (1.11 to 1.29)
Connective tissue disease/rheumatic disease	0.98 (0.89 to 1.07)	1.01 (0.80 to 1.29)	1.06 (0.88 to 1.28)
Peptic ulcer	1.57 (1.35 to 1.84)	1.08 (0.74 to 1.56)	1.22 (0.85 to 1.74)
Mild liver disease	1.18 (1.09 to 1.27)	1.04 (0.88 to 1.23)	0.98 (0.83 to 1.16)
Moderate or severe liver disease	0.61 (0.51 to 0.73)	0.75 (0.56 to 1.00)	0.45 (0.26 to 0.76)
Diabetes without chronic complications	0.81 (0.78 to 0.84)	0.79 (0.73 to 0.87)	0.91 (0.83 to 0.98)
Diabetes with chronic complications	0.61 (0.54 to 0.68)	0.63 (0.49 to 0.81)	0.72 (0.57 to 0.91)
Paraplegia and hemiplegia	0.96 (0.91 to 1.02)	0.88 (0.76 to 1.01)	1.01 (0.89 to 1.14)
Renal disease			

Table 2 (*continued*)

Variable	All patients (n = 374,244)	Patients admitted to critical care (n = 34,239)	In survivors on readmission (n = 289,753)
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
	0.90 (0.87 to 0.92)	0.85 (0.80 to 0.91)	0.98 (0.93 to 1.03)
Primary cancer	1.02 (0.95 to 1.10)	0.63 (0.50 to 0.79)	1.26 (1.09 to 1.45)
Metastatic carcinoma	1.49 (1.38 to 1.60)	0.84 (0.59 to 1.18)	1.39 (1.16 to 1.65)
Obesity	1.19 (1.13 to 1.25)	0.84 (0.76 to 0.92)	1.33 (1.20 to 1.47)

The model for all patients is based on data for 343,237 patients with complete data, the model for critical care patients is based on data for 30,782 patients with complete data and the model for readmissions in survivors is based on data for 264,178 patients with complete data. The models are multilevel, multivariable models that include each of the variables listed as fixed effects and for NHS hospital trust as a random effect. A stable odds ratio for the comorbidity HIV/AIDS could not be calculated due to small numbers.

[a] For Charlson Comorbidity Index items, the reference category is patients without the specified comorbidity. For Charlson Comorbidity Index items relating to liver disease, diabetes and cancer, three mutually exclusive categories were used.

picked up through a dedicated prospective screening programme [5,25,26]. Nevertheless, our study is a record of routine clinical practice during the COVID-19 pandemic and cases where VTE was a major complication of the hospital stay will have been identified.

We identified a rate of VTE in survivors within 42 days of discharge of 1.3%. Previous reports of the COVID-19 post-discharge rate of VTE vary. Roberts et al. [27] reported nine episodes of VTE at 42-day post-discharge from 1877 patients studied, giving an incidence rate of 0.5%, at two English hospitals during spring 2020. Giannis et al. [28], reported a 90-day post-discharge incidence of VTE of 1.6% in 4906 New York state COVID-19 patients also from spring 2020. A meta-analysis of 11 studies (largest: 8983 patients) that investigated VTE incidence post-hospital discharge calculated a rate of 1.8% (95% CI 0.8 to 4.1) [29]. The relatively wide confidence limit reflects different study methodology, approaches to case identification, timing and setting. Our results are likely to represent an under-estimate, for the reasons given above. Additionally, VTE diagnosed and managed post-discharge solely in an ambulatory setting will not be captured in HES.

VTE was associated with a higher adjusted in-hospital mortality rate, particularly in younger age groups and in patients of Asian ethnicity, with diabetes, liver disease and HIV/AIDS. Although other associations follow previous identified patterns [8,9], the link between VTE and mortality in younger patients is striking. In older patients underlying comorbidities and frailty are likely to be a key driver for high mortality.

Although hospital stay is generally longer for patients admitted to critical care than patients who remain on a ward setting, the greater length of stay for critical care patients with VTE is notable [10]. For these most severely ill patients, VTE is likely to represent a significant complication during their stay. However, there are a number of potentially confounding factors in the relationship, most notably greater disease severity. A prospective study looking at disease severity, the timing of VTE in relation to critical care admission and overall length of stay would be of particular interest.

10.1. Strengths and limitations

As an England-wide dataset, HES is able to identify readmissions to a trust other than the index admission trust. Furthermore, the completeness of our dataset will help to minimise collider bias when considering hospital populations [30]. We emphasise that our findings should not be

Table 3
Mortality rate for patients with and without venous thromboembolism during the index admission.

Variable	Patients with venous thromboembolism ($n =$ 13,525)	Patients without venous thromboembolism ($n =$ 360,719)
Age band (years)		
18–39	38 (5.2%)	509 (1.4%)
40–49	118 (9.6%)	1262 (4.2%)
50–59	357 (14.4%)	4278 (8.7%)
60–69	753 (24.9%)	9839 (17.8%)
70–79	939 (30.9%)	20,875 (28.2%)
≥80	1204 (39.9%)	44,319 (37.9%)
Sex (missing = 46)		
Female	1268 (23.8%)	33,578 (19.7%)
Male	2140 (26.1%)	47,499 (24.9%)
Deprivation quintile (missing 8072)		
1 (most deprived)	886 (25.8%)	19,526 (20.8%)
2	716 (23.6%)	17,229 (21.9%)
3	589 (24.9%)	15,845 (23.6%)
4	640 (27.7%)	14,433 (23.9%)
5 (least deprived)	485 (24.3%)	12,738 (24.1%)
Ethnicity (missing = 24,072)		
White	2513 (26.0%)	66,595 (24.4%)
Black	177 (19.8%)	2612 (16.8%)
South Asian	233 (30.4%)	4627 (18.0%)
Other Asian	63 (22.7%)	1150 (14.2%)
Mixed	26 (19.7%)	422 (13.0%)
Other	116 (20.4%)	1762 (14.1%)
Comorbidity		
Peripheral vascular disease	250 (35.6%)	6590 (35.5%)
Chronic heart failure	666 (44.2%)	20,199 (41.2%)
Acute myocardial infarction	331 (38.5%)	11,442 (34.9%)
Cerebrovascular disease	427 (37.8%)	11,228 (33.3%)
Dementia	364 (37.8%)	17,863 (38.8%)
Pulmonary disease	1009 (30.0%)	24,933 (26.8%)
Connective tissue disease	125 (31.4%)	3198 (28.0%)
Peptic ulcer	52 (32.3%)	812 (30.8%)
Diabetes without chronic complications	874 (30.3%)	23,463 (27.2%)
Diabetes with chronic complications	101 (38.4%)	3213 (29.8%)
Hemiplegia/ paraplegia	95 (33.1%)	2484 (31.0%)
Renal disease	692 (40.3%)	24,529 (37.6%)
Primary cancer	250 (36.1%)	6898 (36.6%)
Metastatic carcinoma	303 (44.3%)	3955 (36.7%)
Mild liver disease	151 (22.2%)	2523 (19.3%)
Moderate/severe live disease	75 (60.0%)	1692 (43.2%)
HIV/AIDS	11 (40.7%)	50 (11.6%)
Obesity	378 (21.6%)	7380 (18.8%)

Percentages refer to the proportion of patients dying relative to all patients with/without venous thromboembolism in that group.

extrapolated to non-hospital populations.

Other than those already acknowledged, our study has a number of limitations. The HES dataset relies on individual hospital trusts compiling data accurately and in a consistent manner. Systems for data collection will have been put under strain during the pandemic. HES does not provided detailed information on how acutely unwell the patient was on presentation therefore we are unable to adjust for these factors. Additionally, there are no data available regarding the extent of any PE and we are therefore unable to differentiate between in-situ thrombosis or 'immunothrombosis' and true PE. Information regarding medications prescribed such as thromboprophylaxis is not available. Nevertheless, VTE prevention practice is well-established in England, and it is likely most patients hospitalised with COVID-19 received thromboprophylaxis unless actively bleeding [31,32].

Our study period was chosen to reflect the first and second pandemic waves in England. Changes in patient management options since this time, high levels of vaccination, the restart of elective surgery and changes in the nature of the dominant SARS-Cov-2 variant circulating have all impacted on the demographic and disease profile of people admitted to hospital with COVID-19 and may have impacted on the incidence of VTE and the profile of those diagnosed with VTE [33]. Although data on vaccination status are not available in the HES dataset, our cohort are likely to be almost entirely unvaccinated or, if vaccinated, with limited protection, given relatively slow initial roll-out of vaccinations in England, the time taken from vaccination to peak antibody development and the time from infection to hospitalisation. A previous study by members of our team tends to confirm that by the end of March 2021 the impact of vaccination on the profile of those admitted to hospital was minimal [11]. The incidence of VTE in COVID-19 patients, the profile of patients with VTE and their outcomes should continue to be monitored to inform practice and service delivery.

11. Conclusions

Our exploratory analysis of a large administrative database has allowed us to identify a number of factors associated with VTE that would be difficult to identify from analysis of smaller datasets. The patterns of VTE and VTE-related in-hospital mortality across age groups are particularly interesting. Clinicians should be aware of the risk of VTE in patients hospitalised with COVID-19, even when routine thromboprophylaxis has been given [4,5], and that VTE is associated with increased mortality and extended hospital stay.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval

Ethical approval was not sought for the present study because it did not directly involve human participants. This study was completed in accordance with the Helsinki Declaration as revised in 2013.

Informed consent to participate

Informed consent was not sought for the present study because it was an analysis of routine clinical data.

Consent to publish

All authors consent to publication.

Contributions

This study was designed and organised by AVN, LR, RA, TWRB and WKG. Data cleaning, analysis and writing of the first draft was by WKG, supported by AVN, LR and RA. All authors critically reviewed the manuscript and agreed to submission of the final draft.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2022.03.017.

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