Twelve-month risk of thromboembolic events in COVID-19 hospital survivors in Scotland

Science Letter

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COVID-19 may predispose patients to arterial and venous thrombotic disorders due to endothelial dysfunction and platelet activation [1]. High rates of in-hospital arterial/venous thromboembolism have been reported [2] and are likely to persist post-discharge. Current UK guidelines suggest prophylactic anticoagulation for a minimum of 7 days, including after hospital discharge [3]. A recent trial found benefit in extending prophylaxis for 35 days after discharge in high-risk patients [4]. We aimed to identify the risk of arterial/venous thromboembolism in a national population in the 12 months after hospital discharge following COVID-19 in order to inform prophylaxis strategies, including anticoagulation decisions and duration.

We used routine healthcare data to identify all COVID-19 hospital survivors from the adult Scottish population of 5.5 million and without documented contraindications to anticoagulation (online Supporting Information, Appendix S1), discharged before 23 August 2021. All patients were followed-up until 23 September 2021 or until

Table 1 Cohort of Scottish hospital COVID-19 survivors without documented contraindications to anticoagulation (n = 20,236) stratified by IMPROVE score. Values are median (IQR [range]) or number (proportion). Counts <5 have been redacted.

IMPROVE score	1 n = 7494	2–3 n = 10,844	4+ n = 1898
Age; y	47 (36–54 [18–60])	73 (64–82 [18–60])	75 (57–83 [18–99])
Sex; male	3736 (49.9%)	5244 (48.4%)	1026 (54.1%)
Scottish Index of Multiple Deprivation 2020 quintile			
1 (most deprived)	2410 (32.2%)	3299 (30.4%)	548 (28.9%)
2	1782 (23.8%)	2596 (23.9%)	451 (23.8%)
3	1248 (16.7%)	1916 (17.7%)	335 (17.7%)
4	1116 (14.9%)	1586 (14.6%)	277 (14.6%)
5 (least deprived)	916 (12.2%)	1416 (13.1%)	286 (15.1%)
(Missing)	22 (0.3%)	31 (0.3%)	<5 (<0.1%)
Ethnicity			
White	5737 (76.6%)	9398 (86.7%)	1764 (92.9%)
Asian, Asian Scottish or Asian British	418 (5.6%)	221 (2.0%)	19 (1.0%)
African	76 (1.0%)	22 (0.2%)	<5 (<0.1%)
Other	197 (2.6%)	89 (0.8%)	12 (0.6%)
(Missing)	1066 (14.2%)	1114 (10.3%)	102 (5.4%)
Source of COVID-19			
Community	6792 (90.6%)	8426 (77.7%)	1334 (67.1%)
Nosocomial	208 (2.8%)	1849 (17.1%)	447 (23.6%)
(Missing)	544 (7.3%)	569 (5.2%)	117 (6.2%)
COVID-19 wave			
1st	1443 (19.3%)	2684 (24.8%)	472 (24.9%)
2nd	4290 (57.2%)	7053 (65.0%)	1228 (64.7%)
3rd	1761 (23.5%)	1107 (10.2%)	198 (10.4%)
Number of Charlson comorbidities			
0	4780 (63.8%)	3348 (30.9%)	110 (5.8%)
1	1966 (26.2%)	3433 (31.7%)	608 (32.0%)
2+	748 (10.0%)	4063 (37.5%)	1180 (62.2%)

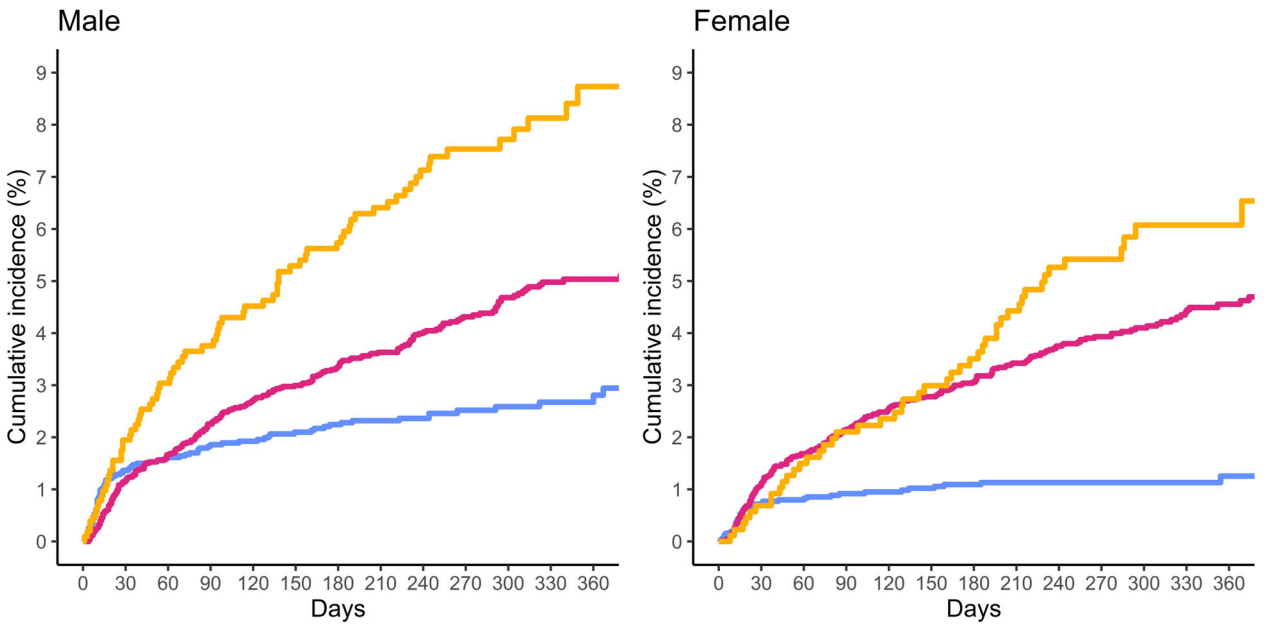

Figure 1 Cumulative incidence of arterial/venous thromboembolism mortality/readmission composite stratified by sex at birth and IMPROVE score (blue, 1; red, 2–3; yellow, 4+). Overall incidence at 35 days was 1.2% (95%CI 1.1–1.4%) and at 12 months was 4.1% (95%CI 3.8–4.5%); n = 20,236.

death. Approval for access to datasets was granted by the Public Benefit and Privacy Panel for Health and Social Care. Our primary outcome was a composite of mortality or hospital readmission for arterial/venous thromboembolism (online Supporting Information, Appendix S1). We used cumulative incidence, accounting for competing risk events, to report mortality and time to first readmission. We stratified our findings by sex and the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) associative score, used to identify high venous thromboembolism risk in acutely ill medical patients for extended thromboprophylaxis (low (0–1), moderate (2–3) and high (4+) risk) [5]. The IMPROVE score comprises seven criteria: previous VTE; known thrombophilia; lower-limb paralysis/paresis; history of cancer; immobilisation ≥ 1 day; critical care stay; and age > 60 y (online Supporting Information, Table S1). The dataset was cleaned and analysed using R v3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Cell counts < 5 were suppressed.

Between 1 February 2020 and 23 August 2021, 22,969 patients were discharged alive from hospital after admission with COVID-19 in Scotland; 22,230 had no contraindications to anticoagulation (Table 1, online Supporting Information, Table S2). The IMPROVE score classified 7494 (37.0%) patients as low risk, 10,844 (53.6%) as moderate risk and 1898 (9.4%) as high risk of VTE. Patients in the high-risk group were older (age 80+ y: high risk 35.1% vs. low risk < 0.1%), and had more comorbidities (2+ Charlson comorbidities: high risk 62.2% vs. low risk 10.0%). Less than 0.1% of the low-risk group were admitted to ICU during their index admission, compared with 19.7% of the moderate-risk group and 10.1% of the high-risk group.

The overall cumulative incidence for arterial/venous thromboembolism was 1.2% (95%CI 1.1 - 1.4%) at 35 days and 4.1% (95%CI 3.8 - 4.5%) at 12 months (Fig. 1, online Supporting Information, Figs. S1 and S2); however, this rose to 2.3% (95%CI 1.7 - 3.0%) at 35 days and 7.5% (95%CI 6.2 - 8.9%) for patients in the high-risk group, and was consistently higher for men than women. Pulmonary embolism was the commonest event resulting in readmission or death across all risk strata (online Supporting Information, Table S3). The arterial/venous thromboembolism events resulting in readmission were significantly higher than those causing death. The rate of events was similar across all strata for the first 30 days (Fig. 1), after which there was a plateau in the low-risk group. However, there was no similar fall in the moderate- or high-risk groups, and the majority of events occurred after 35 days post-discharge.

The risk of arterial/venous thromboembolism after discharge from hospitalisation with COVID-19 was high, and considerably greater across all IMPROVE strata compared with the cohort in which the score was derived when restricted to a comparable outcome (VTE 0.4% at 3 months post discharge vs. our cohort VTE incidence of

1.6% (95%CI 1.4 - 1.7%)) [5]. Rates were lower than observed in the enriched control arm of Nishiga et al. [1], where asymptomatic arterial/venous thromboembolism detected by screening accounted for a third of the events.

A strength of our study is its population-based approach in a real-world setting, where routine healthcare data can enable identification of clinically significant events. We were unable to account for in-hospital management, such as treatment with steroids or tocilizumab.

Even in the low-risk group, the 2.0% risk of arterial/venous thromboembolism at 12 months was high enough to justify offering patients anticoagulation treatment, in line with treatment thresholds for other conditions with thrombotic risk such as atrial fibrillation [6]. Consideration should be given to the role of anticoagulation in all patients with severe COVID-19 when discharged from hospital, with a shared decision-making approach taken when balancing risks of arterial/venous thromboembolism against bleeding. The mechanism of arterial/venous thromboembolism in COVID-19 may include immunothrombosis in addition to the non-immunological venous thromboembolism seen in other conditions, raising the possibility that anticoagulants with anti-inflammatory properties such as heparins may be more effective than direct oral anticoagulants [7]. Although the incidence in the lowest risk group plateaued within the first month, higher risk groups showed no such reduction, and longer-term anticoagulation should be considered for high-risk patients, potentially in line with guidelines suggesting a minimum of 3 months for a provoked pulmonary embolism [8].

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Supporting Information

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

Appendix S1. Methods.

Figure S1. Cumulative incidence for arterial/venous thromboembolism (AV-TE) specific readmission and AV-TE specific mortality up to 12 months post hospital discharge.

Figure S2. Cumulative incidence for AV-TE specific mortality/readmission stratified by individual strata of IMPROVE score.

Table S1. Modified IMPROVE Score, used by MICHELLE trial Investigators.

Table S2. Comorbidities and treatment of Scottish hospital COVID-19 survivors without documented contraindications to anticoagulation.

Table S3. Cumulative incidence at 12 months for readmission, mortality and composite of readmission and mortality from overall arterial/venous thromboembolism, stroke, acute myocardial infarction, pulmonary embolism, other arterial/venous thromboembolism.