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Authors Contribution

Each named author has substantially contributed to conducting the underlying research and drafting this manuscript. AE, TV, HN, RS and MJ developed the idea. The project was designed by AE and MJ with input from HN, RS. All Authors collected the data. MTJ analysed the data. AE and MJ prepared the draft manuscript. All authors contributed to manuscript preparation and revision.
Arterial and venous thromboembolism in critically ill, COVID 19 positive patients admitted to Intensive Care Unit

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Background

On 11th March 2020 the World Health Organization declared the international spread of the SARS-CoV-2 virus to represent a pandemic.(1) Thus far more than 160 million cases has been confirmed worldwide with nearly 4.5 million cases of SARS-CoV-2 infection have been confirmed in the UK and with high numbers of patients requiring respiratory support, the outbreak converted the entire UK healthcare system into the Critical Care without walls.(2,3) The mortality in patients with COVID varies between countries and healthcare systems and has been reported between 0.1% and 19.6%. (4) Our local Intensive Care Unit (ICU) audit indicates that once the patient requires organ support, the mortality is as high as 30% which is similar to the 25% overall mortality in a recently published systematic review.(5)

There is evidence that the underlying patho-mechanism of COVID-19 is related to hypercoagulable state and endothelial dysfunction which results in pan-vascular events: thrombosis within small and large vessels, resulting in deep vein thrombosis (DVT), pulmonary embolisms, strokes and myocardial infarctions.(6) There have been reports of thrombosis within other vascular beds including upper and lower limbs as well as visceral circulation. This is likely to be a result of sepsis-induced coagulopathy (associated with the cytokine storm, not the cytokine storm itself) and viral replication leading to endothelial injury.(7–10)

The incidence of arterial/venous thromboembolism has been recently reported but the rates have been compared with non-COVID-19 patients or historical populations in only a few papers and therefore, we believe that the scale of the problem is not sufficiently defined.(11,12)

However, recent reports indicate that the incidence of thromboembolic events in patients with SARS-CoV-2 infection might be higher than expected and would require adjusted thromboprophylaxis.(13–15) However, thus far there are significant uncertainties regarding prevention and management of thromboembolic events in patients with COVID-19.

We considered this project to be a hypothesis generating study. The main objective of was to establish
the incidence of acute vascular events and identify potential associations with clinical and demographic
factors in a cohort of ICU patients with confirmed, severe SARS-CoV-2 infection. The secondary
objectives were to provide a basis necessary for ad hoc adjustment of clinical practice and to highlight
areas for potential research studies aiming to optimise thromboprophylaxis and medical management
of thromboembolic events.

Methods

We followed STROBE Statement for cross-sectional studies in preparation of this manuscript.(16)

This was a retrospective, single-centre (University Hospitals Birmingham NHS Foundation Trust;
UHB), multi-site cohort study using routinely collected data, conducted within the clinical audit
framework (Audit numbers); no intervention was performed, and patients were not contacted outside
their routine clinical care. Therefore, a specific ethical approval was not required, and patient consent
was not sought in line with guidance from the UK Health Research Authority and UK Policy
Framework for Health and Social Care Research.

We collated the data from three hospitals in Birmingham Metropolitan area for all consecutive patients
admitted to ITU during the peak of COVID-19 pandemic in the UK, between 01/04/2020 and
30/04/2020. We also collected data from the corresponding pre-COVID period in 2019 (01/04/2019 –
30/04/2019) and used it to estimate excess events. Definitions and type of data collected are detailed in
the supplementary file.

Outcomes

Primary outcome

The primary outcome was defined as a composite outcome of acute arterial and venous events, which
included: 1) upper and/or lower limb arterial thrombosis or embolus, 2) exacerbation of peripheral
arterial occlusive disease (PAOD) with progression to critical limb ischaemia (CLI), 3) stroke or
transient ischaemic attack (TIA), 4) visceral malperfusion, 5) thrombosis of AV fistula, 6) venous
thrombotic events (DVT); pulmonary embolism (PE), visceral veins thrombosis, thrombophlebitis).

Secondary outcomes

The secondary outcome was 30-day mortality. We also studied associations of demographic and clinical factors with the primary and secondary outcome, and temporal changes in the biochemical and clotting parameters.

Verification of outcomes

Primary outcome was validated manually by the direct clinical care team members. Cases where the outcome was not certain were verified by senior clinicians. Survival status was verified by cross-referencing local electronic patient record with the NHS-wide mortality database (Primary Care Mortality Database, Spine, NHS Digital) derived from death records from the Office for National Statistics.

Statistical analysis

The statistical analysis was performed in R environment (R version 4.0.3, The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org) using pre-specified data analysis plan. Data characteristics were assessed using dplyr package and data missingness was assessed using naniar package. Missing data were treated by pairwise deletion.

Continuous variables were presented as median [interquartile range; IQR] unless stipulated otherwise; categorical data were presented as frequencies (%) with 95% confidence intervals (95%CI) if required. Student’s t-test and Wilcoxon rank-sum test were used to compare continuous data. Pearson’s chi-squared test and Fisher’s exact test with continuity correction were used to analyse categorical data. Haldane-Anscombe correction was used when appropriate. Multi-variate explanatory model was built using purposeful, manual selection of covariates with univariate p<0.1, taking into consideration the quality of the data and clinical judgement. Effect size was presented as odds ratio (OR) with 95%CI and categorised as “small” (OR<1.5), “medium” (1.5=<OR<5.0) and “large” (OR>=5.0).
Results

Cohort characteristics

During April 2020 the peak of the pandemic in the UK, 317 patients were treated and discharged (alive or deceased) from ITU at three sites of the University Hospitals Birmingham NHS Foundation Trust. The median age was 56 years [47, 66], and 94 of them (29%) were female. Patients with white Caucasian ethnic background constituted a majority (170; 53.8%) of patients in whom ethnicity was declared (268; 84.5%), followed by Asian (79; 29.55%) and Black (19; 7.1%) ethnic background. Over a half of patients (51.4%) came from the 20% most deprived households, and only 8.9% from the 20% least deprived households in England based on Index of Multiple Deprivations 2019.(17)

Detailed characteristics of comorbid status of patients in the study is shown in Table 1. Hypertension (128/317; 40.4%), diabetes (86/317; 27.1%) and chronic lung disease (46/317; 14.5%) were the most prevalent comorbidities in patients admitted to ITU in April 2020. Smoking status was recorded in 47.5% of patients: 20.7% declared as non-smokers, 24.0% as ex-smokers and 55.3% declared non-smoking status.

Data on VTE prophylaxis was missing in 3 cases (0.9%). VTE prophylaxis was in prescribed in 294 (93.6%) patients; one patient was on bridging therapy (0.3%); VTE prophylaxis was not prescribed in 19 patients (death shortly after admission to ITU or clearly documented contraindications). The DVT prophylaxis regimen was the standard hospital protocol of 40mg of enoxaparin once a day. Data characteristics are detailed in the supplemtary file.

Prevalence of COVID-19 in ITU patients

During April 2020, 198 out of 317 ITU patients were diagnosed with COVID-19 resulting in the period prevalence of 62.5% (56.9-67.8).
D-Dimer levels

The D-Dimer levels were measured in 189 patients (59.6%) in whom there was a clinical suspicion of VTE. The levels were similar in COVID and non-COVID patients (849 [438.0, 3472.5] v. 947 [535.8, 5931.2, p=.589] and were significantly higher in patients who had a thromboembolic event (1,656 [IQR 577.8, 9172.5] v. 826 [IQR 426.5, 2836.5]). The difference in D-Dimer levels between patients with different COVID status and thromboembolic events were not statistically significant (ANOVA, df=5, F=0.893, p=.487).

Thromboembolic events

Arterial and venous thromboembolic events occurred in 75 patients treated on ITU in April 2020 (event rate 23.7% (19.1-28.7)). Detailed distribution of thromboembolic events is shown in Table 2.

Arterial events occurred in 26 out of 317 patients (8.2%). This rate was higher than in comparable months of 2019, however, the difference was not statistically significant (OR 1.22, 0.69-2.10, p=.546).

In seven patients’ arterial events coincided with 3 deep and 2 superficial vein thrombosis, and 3 pulmonary embolisms.

COVID-19 status was not associated with arterial events, and neither was the best medical therapy. However, arterial events were associated with increased 30-day mortality. This was significant irrespective of COVID-19 status (all patients: 65.4% v. 30.2%; OR 4.34, 1.75-11.49, p<.001; COVID-19 positive only: 64.7% v. 34.3%; OR 3.49, 1.12-12.08, p=.018).

DVT occurred in 20 patients (6.3%). This rate was significantly higher than in corresponding months of 2019 (16/555, 2.88%; OR 2.27, 1.10-4.75, p=.020).

Amongst patients with DVT, 3 had simultaneous arterial events, 4 had simultaneous PEs and two had thrombophlebitis (one coinciding with arterial event).

In the studied cohort of patients, DVT was not associated with COVID-19 status, demographic factors,
comorbid status, or best medical therapy or thirty-day mortality. However, we observed an association of DVT rate with personal history of VTE (OR 5.41, 1.15-20.34, p=.016), and regular prescription for DOAC (OR 5.19, 1.31-17.81, p=.010), but not warfarin, before index admission.

Thirty-four pulmonary embolisms occurred during the observation period (10.7%). Pulmonary embolisms occurred almost 4 times more often than in 2019 (OR 3.80, 2.02-7.38, p<.001).

In patients with diagnosis of PE, 7 events coexisted with 3 arterial events and 4 DVT.

There was an association between the diagnosis of pulmonary embolisms, and diagnosis of COVID-19 (OR 3.80, 1.54-11.64, p=.004), personal history of VTE (OR 7.03, 2.34-20.15, p<.001), lactate on admission to ITU (Cohen's d = -0.19 (effect negligible), p=.023). Pulmonary embolism was also associated with a higher risk of 30-day mortality (OR 3.30, 1.60-7.01, p=.002).

Univariate analysis demonstrated that age, but not ethnicity or social deprivation, was the demographic factor associated with development of arterial and venous thromboembolic events. Smoking status was associated with thromboembolic events (non-smokers and ex-smokers v. current smokers: OR 5.3, 1.22-48.3, p=.015) but there was a substantial missingness within this variable and this factor was not used in multivariate model.

A diagnosis of COVID-19 (clinical or laboratory-based) and personal history of VTE, but none of the recorded comorbidities were associated with development of thrombotic events. A new onset renal failure requiring acute dialysis was also associated with the diagnosis of VTE, but the direction of this association could not be ascertained using our data.

Amongst regular medication, only antiplatelet agents and direct oral anticoagulants were associated with the diagnosis of arterial and venous thromboembolism. VTE prophylaxis was uniformly applied and was not associated with the risk of VTE.

Multivariate analysis showed that only personal history of VTE (OR 14.0, 3.98-54.34, p<.001), pre-admission regular antiplatelet agent (OR 0.25, 95%CI 0.07-0.71, p=.018), COVID19 status (OR 2.64,
1.29-5.77, \( p = .011 \)), a need for renal replacement therapy (OR 2.40, 1.21-4.72, \( p = .011 \)) and lactate level on admission to ITU (OR 1.17, 1.03-1.33, \( p = .013 \)) were independently associated with the diagnosis of arterial and venous thromboembolic events figure 1 and figure 2. Tables and figures detailing the multivariate analysis are included in the supplementary file.

**Discussion**

We observed increased rates of DVT and PE, with no excess arterial events or thrombophlebitis in patients admitted to ITU in 2020 compared with 2019. When we compared the non COVID patients in the 2020 cohort versus the 2019 cohort there was no statistically significant difference in the incidence of the VTE. In patients with positive COVID-19 status, 30-day mortality was associated with arterial events and pulmonary embolism, but not DVT or thrombophlebitis.

There was no association of arterial events with COVID-19 status. Similarly, the rates of deep and superficial venous thrombosis were not associated with COVID-19 in our cohort. However, there was a significant association of pulmonary embolism with COVID-19 status (OR 3.90, 1.43-13.29, \( p = .006 \)). This can be explained by under diagnosis of asymptomatic of deep and superficial venous thrombosis.

The incidence of acute arterial events is notoriously difficult to establish, since it is often not recognised and not treated promptly in particular if the symptoms are mild. Using a large prospective cohort Howard *et al.* demonstrated the incidence of acute arterial events of around 0.4%.(18) A large retrospective analysis of patients with COVID-19 from New York involving over 12 thousand patients failed to explicitly provide the point prevalence of acute arterial events, but the number of patients presenting during observation period represents the rate of ~0.36%.(12) Although done in different geographical locations, encompassing different populations, and different healthcare systems, the results look suspiciously similar, and point towards absence of excess events. We believe that the perceived increase in acute arterial events is caused by the high number of COVID-19 cases and increased attentiveness of vascular surgeons, and may represent observer bias.

The increased incidence of VTE (mainly PE) in patients with COVID-19 has been demonstrated
previously. However, the rates vary considerably depending on the cohort studied. A recent meta-analysis demonstrated a considerable geographical variability with reports from Germany showing the incidence of around 20% and countries like France and Netherlands reporting the incidence of VTE of up to 40%. The incidence was higher in critically ill patients than in patients not requiring higher level of care, or patients not requiring hospitalisation. The post-discharge incidence of VTE was also low, but the baseline incidence of VTE in the studied ethnic group is generally low. These differences in VTE rates are probably related to detection levels and logistical problems with obtaining appropriate imaging.

Our team performed a comparative audit looking at patterns of referral for compression ultrasound scans and rates of DVT. The referral pattern during audited months (March and April 2020) was very similar to that in 2019 and so was the detection rate. Unlike in present study, we detected excess DVT events. However, it is plausible that the detection rate in patients on ITU was hampered by difficulties with logistics of compression ultrasound (CUS) scans. We believe that training of the ITU staff in bedside CUS may aid early diagnosis and treatment of DVT.

Patients admitted to ITU who subsequently developed arterial events had high mortality rates irrespective of COVID status. In these patients, any intervention for acute arterial event was either deemed inappropriate due to unfavourable prognosis irrespective of arterial event or absence of indications for surgical intervention (e.g. digital ischaemia). In addition, early reports from other centres indicated that mortality associated with surgical intervention in patients with moderate and severe SARS-CoV-2 infection was associated with high mortality. The approach to acute arterial events in critically ill patients, in general, varies considerably between individual units, and even individual surgeons. There is no consensus on this issue and no advice is available in the most recent European Society guidelines either.

Arterial events coincided with venous thromboembolism in 26.9% of cases (7/26), and 3 out of 20 patients with DVT developed associated arterial events (15.0%). Thrombosis (mainly venous) related to viral infection is not unique for SARS-CoV-2. Other viruses, such as H1N1, SARS and MARS were
shown to induce venous thrombosis. However, presence of SARS-CoV-2 infection cannot be proven as a sole factor responsible for coexisting arterial and venous events. One of possible explanations for the arterial events coinciding with VTE could be the presence of patent foramen ovale (PFO). This developmental cardiac defect is occasionally blamed for paradoxical emboli. The prevalence of PFO in general population is estimated to be between 25% and 27% (27) and would constitute a plausible explanation for observed arterial phenomena as described previously. (28–30)

Various mechanisms of thromboembolism in patients with SARS-CoV-2 infection have been suggested. (31) Some proposed alterations in coagulation profiles and underlying genetic problems. The latter would be consistent with our findings showing a significant association of the diagnosis of DVT with the personal history of VTE. However, systemic hypercoagulation is not novel, and not exclusive to SARS-CoV-2. Viral coagulopathy has been noted in other systemic viral infections such as SARS, MARS and H1N1, all specifically causing intrapulmonary thrombi. (32,33)

The best way to assess how sick the patients were was APACHE II Score ("Acute Physiology And Chronic Health Evaluation II"). Unfortunately this was not routinely used in all units. We attempted to manually curate (not to derive/calculate) the clinical data guiding the management of patients admitted to ITU. Unfortunately, we had an unacceptable data missingness and had to remove this from the dataset early. Have we had this data, we still would have not been able to tell the direction of any possible association (i.e. patients were sicker therefore developed PE or they developed PE and therefore were sicker -both being plausible).

We demonstrated that regular antiplatelet agent prior to admission was associated with reduced risk of thromboembolic events. It is plausible that the association of antiplatelet agents with lower prevalence of thrombosis seen in our study relates to prevention of the platelet aggregation in the asymptomatic and paucisymptomatic phase of the disease and prevents propagation of thrombosis to large VTE. Our results contradict those published by Sahai et al. who demonstrated a prothrombotic effect of aspirin. (34) In their analysis they combined those who were on aspirin prior to contact, with those who were recently started on it, without considering indications. The direction of the association could
significantly confuse interpretation of the results. All patients who develop stroke and who have no specific contraindications are started on high-dose antiplatelet regimen. If the timing of these two events is not known, it is easy to conclude that aspirin caused the stroke. We believe this is not the case. In our study, we only recorded use of aspirin prior to contact to avoid such problems.

We observed increased risk of DVT in patients on regular prescription of DOAC, but not warfarin. This relationship could be explained by a very short half-life of direct oral anticoagulants compared with warfarin. Warfarin has a different mechanism to DOACs and much longer half-life that can be pathologically extended by severe illness. Therefore, the protection offered by vitamin K inhibitors may last long enough for the appropriate bringing therapy to be instigated when the patient becomes critically ill.

Conclusions

Although COVID-19 virus-related arterial and venous thrombosis does exist, our study does not show increased incidence rate compared with our local pre-pandemic rates. However, there was a significant association of pulmonary embolism with COVID-19 status.

Antiplatelet agents may play a role in prevention of virus-related thromboembolism, but this report does not constitute the evidence supporting their use. We merely reported on a potential signal arising from demonstrated association. Further studies are required to investigate this potentially beneficial effect.

Limitations and bias

We recognise that our study has significant limitations. This was a retrospective audit, and all data relied on accurate recording of clinical details. We chose 1 month, which was our local peak of COVID-19 cases as data collection, was done manually and time consuming. We chose the same period in 2019 as a comparator rather than earlier years to decrease any difference in management of cases in the ITU.

We understand that our sample is not representative of the entire population. However, it represents a population with extremely thorough, high frequency clinical assessment, where the chances of missing
an event are very small. This would really be only limited to asymptomatic cases where the diagnosis
would be fully dependant on imaging. In addition, this sample represents the most severe spectrum of
the COVID-19 where one would naturally expect arterial and venous thrombosis to manifest itself as
widely reported.

On the other hand, the dataset is relatively small, limited by the observation period and the selection of
cohort of interest. This study does not account for the duration of thromboprophylaxis or therapeutic
anticoagulation which could potentially reduce the thromboembolic events. The dataset lacks the
necessary granularity and chronology to make such observations.
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Table 1: Cohort characteristics stratified by YEAR. Comparison on ITU cohorts between March/April 2019 and April 2020. All patients irrespective of COVID-19 status. ACEi – angiotensin converting enzyme inhibitor; aPTT – activated partial thromboplastin time; ARB – angiotensin receptor blocker; IQR – interquartile range; PT – prothrombin time; SD – standard deviation; VTE – venous thrombo-embolism.

| Variable             | Level       | 2019 (n=555) | 2020 (n=317) | p-value |
|----------------------|-------------|--------------|--------------|---------|
| COVID19StatusGRP     | Negative    | 555 (100.0)  | 119 (37.5)   |         |
|                      | Positive    | 0 (0.0)      | 198 (62.5)   | < 0.0001|
| DEATH                | 0           | 455 (82.0)   | 212 (66.9)   |         |
|                      | 1           | 100 (18.0)   | 105 (33.1)   | < 0.0001|
| AGE                  | median [iqr]| 62 [48, 73]  | 56 [47, 66]  | < 0.0001|
| SEX                  | Female      | 215 (38.7)   | 94 (29.7)    |         |
|                      | Male        | 340 (61.3)   | 223 (70.3)   | 0.008677|
| Ethnicity            | Male        | 340 (61.3)   | 223 (70.3)   |         |
|                      | White       | 400 (81.3)   | 170 (63.4)   |         |
|                      | Asian       | 70 (14.2)    | 79 (29.5)    |         |
|                      | Black       | 22 (4.5)     | 19 (7.1)     | < 0.0001|
|                      | missing     | 63           | 49           |         |
| IMD_QUINT            | Q1          | 227 (42.9)   | 161 (51.4)   |         |
|                      | Q2          | 100 (18.9)   | 44 (14.1)    |         |
|                      | Q3          | 82 (15.5)    | 46 (14.7)    |         |
|                      | Q4          | 67 (12.7)    | 34 (10.9)    |         |
|                      | Q5          | 53 (10.0)    | 28 (8.9)     | 0.155293|
|                          | missing | 26 | 4          | median [iqr] | 170 [161, 177] | 170 [164, 178] | 0.023621 |
|--------------------------|---------|----|------------|--------------|----------------|----------------|-----------|
| **Height**               |         |    |            |              |                |                |           |
|                          | missing | 58 | 50         |              |                |                |           |
| **Weight**               | median [iqr] | 76 [65, 90] | 81.2 [70.7, 95.0] | < 0.0001 |
|                          | missing | 55 | 51         |              |                |                |           |
| **Body Mass Index**      | median [iqr] | 26.4 [23.4, 30.3] | 27.8 [24.9, 31.6] | 0.000230 |
|                          | missing | 60 | 51         |              |                |                |           |
| **IHD**                  | No      | 465 (83.8) | 287 (90.5) |              |                |                |           |
|                          | Yes     | 90 (16.2) | 30 (9.5)   | 0.007318     |                |                |           |
| **Atrial Fibrillation**  | No      | 511 (92.1) | 295 (93.1) |              |                |                |           |
|                          | Yes     | 44 (7.9)  | 22 (6.9)   | 0.691055     |                |                |           |
| **CCF**                  | No      | 519 (93.5) | 309 (97.5) |              |                |                |           |
|                          | Yes     | 36 (6.5)  | 8 (2.5)    | 0.015920     |                |                |           |
| **VTE**                  | No      | 520 (93.7) | 300 (94.6) |              |                |                |           |
|                          | Yes     | 35 (6.3)  | 17 (5.4)   | 0.676454     |                |                |           |
| **Hypertension**         | No      | 354 (63.8) | 189 (59.6) |              |                |                |           |
|                          | Yes     | 201 (36.2) | 128 (40.4) | 0.251326     |                |                |           |
| **CVA**                  | No      | 523 (94.2) | 300 (94.6) |              |                |                |           |
|                          | Yes     | 32 (5.8)  | 17 (5.4)   | 0.923753     |                |                |           |
| **Diabetes Mellitus**    | No      | 454 (81.8) | 231 (72.9) |              |                |                |           |
|                          | Yes     | 101 (18.2) | 86 (27.1)  | 0.002655     |                |                |           |
| Variable   | No              | (%) | Yes              | (%)   | p-value |
|------------|-----------------|-----|------------------|-------|---------|
| CLD        |                 |     |                  |       |         |
| No         | 486 (87.6)      | 271 (85.5) | 69 (12.4)      | 46 (14.5) | 0.442156 |
| Yes        |                 |     |                  |       |         |
| MALIGNANCY |                 |     |                  |       |         |
| No         | 381 (69.0)      | 281 (88.6) | 16 (2.9)       | 8 (2.5)   |         |
| Not confirmed | 155 (28.1) | 28 (8.8) | < 0.0001        |       |
| Yes        |                 |     |                  |       |         |
| missing    | 3               | 0   |                  |       |         |
| SMOKING    |                 |     |                  |       |         |
| Non-smoker | 111 (39.4)      | 83 (55.3) | 94 (33.3)      | 31 (20.7) |         |
| Current smoker | 77 (27.3) | 36 (24.0) | 0.003345        |       |
| Ex-smoker  |                 |     |                  |       |         |
| missing    | 273             | 167 |                  |       |         |
| APA        |                 |     |                  |       |         |
| No         | 372 (71.3)      | 257 (85.1) | 150 (28.7)     | 45 (14.9) | < 0.0001 |
| Yes        |                 |     |                  |       |         |
| missing    | 33              | 15  |                  |       |         |
| DOAC       |                 |     |                  |       |         |
| No         | 481 (92.1)      | 276 (91.4) | 41 (7.9)       | 26 (8.6)  | 0.802775 |
| Yes        |                 |     |                  |       |         |
| missing    | 33              | 15  |                  |       |         |
| WARFARIN   |                 |     |                  |       |         |
| No         | 498 (95.4)      | 292 (96.7) | 24 (4.6)       | 10 (3.3)  | 0.475923 |
| Yes        |                 |     |                  |       |         |
| missing    | 33              | 15  |                  |       |         |
| STATIN     |                 |     |                  |       |         |
| No         | 338 (64.8)      | 212 (70.2) | 184 (35.2)     | 90 (29.8) | 0.127838 |
| Yes        |                 |     |                  |       |         |
| missing    |                 |     |                  |       |         |
|                  | Missing | No   | Yes  | \( p \)  |
|------------------|---------|------|------|----------|
| **ACE**          | 33      | 375  | 147  | 0.025478 |
| **Beta Blocker** | 33      | 411  | 111  | 0.397312 |
| **SURG_GRP**     | 7       | 163  | 385  | < 0.0001 |
| **Haematocrit**  | 0       | 0.3  | 0.4  | < 0.0001 |
| **Platelet**     | 0       | 210  | 242.5| < 0.0001 |
| **Activated partial thromboplastin time** | 28 | 27.4 [25.2, 31.2] | 30.4 [27.4, 33.4] | < 0.0001 |
| **Prothrombin time** | 64 | 13.6 [12.5, 15.7] | 14.4 [13.2, 15.6] | 0.380160 |
| **D Dimer**      | 530     | 1,136 [558, 3,445] | 874 [449, 3,538] | 0.820550 |
|            | median [iqr] |            |            |        |
|------------|--------------|------------|------------|--------|
| Neutrophils| 9.4 [5.6, 13.7] | 8.5 [5.9, 11.7] | 0.041200   |        |
| Lymphocytes| 1 [0.6, 1.6] | 1 [0.7, 1.6] | 0.226872   |        |
| Creatinine | 79 [62, 108] | 80 [62, 115] | 0.568150   |        |
| Urea       | 5.8 [4.1, 8.9] | 6 [4.4, 10.1] | 0.309157   |        |
| RRT_GRP     | No          | 502 (90.5) | 248 (78.5) |        |
|             | Yes         | 53 (9.5)  | 68 (21.5)  | < 0.0001 |
| ABG Lactate | median [iqr] | 1.6 [1.1, 2.7] | 1.4 [1.1, 2.1] | 0.018191 |
| ABG PaO2    | median [iqr] | 15.7 [11.1, 24.2] | 10.5 [8.4, 14.6] | < 0.0001 |
| ABG FiO2    | median [iqr] | 0.2 [0.2, 0.4] | 0.4 [0.2, 0.7] | < 0.0001 |
| VTE Prophylaxis | Mechanical | 18 (3.3) | 0 (0.0) |        |
| Group       | No          | 69 (12.5) | 19 (6.1)  |        |
|             | Treatment   | 0 (0.0)  | 0 (0.0)   |        |
| Event                  | Yes     | 466 (84.3) | 295 (93.9) | NA   |
|------------------------|---------|------------|------------|------|
|                        | missing | 2          | 3          |      |
| **EVENT**              |         |            |            |      |
| No                     | 493 (88.8) | 242 (76.3) |            |      |
| Yes                    | 62 (11.2) | 75 (23.7)  | < 0.0001   |      |
| Arterial Event Group   |         |            |            |      |
| No                     | 517 (93.2) | 291 (91.8) |            |      |
| Yes                    | 38 (6.8) | 26 (8.2)   | 0.546455   |      |
| **DVTGroup**           |         |            |            |      |
| No                     | 539 (97.1) | 297 (93.7) |            |      |
| Yes                    | 16 (2.9) | 20 (6.3)   | 0.023249   |      |
| Pulmonary Embolism     |         |            |            |      |
| No                     | 538 (96.9) | 283 (89.3) |            |      |
| Yes                    | 17 (3.1) | 34 (10.7)  | < 0.0001   |      |
| Arteriovenous Access   |         |            |            |      |
| Group                  |         |            |            |      |
| No                     | 549 (98.9) | 310 (97.8) |            |      |
| Yes                    | 6 (1.1)  | 7 (2.2)    | 0.302713   |      |

**Abbreviations**:  
- **IHD**: Ischemic Heart Disease  
- **IMD Quint**: Index Of Multiple Deprivation Quintiles  
- **CCF**: Congestive Cardiac Failure  
- **VTE**: Venous Thromboembolism  
- **DOAC**: Direct Oral Anticoagulant  
- **APA**: Antiplatelet Agents  
- **BB**: Beta Blocker  
- **CVA**: Cerebrovascular Accident  
- **CLD**: Chronic Lung Disease  
- **ACE**: Angiotensin-Converting Enzyme Inhibitors  
- **RRT**: Renal Replacement Therapy  
- **ABG**: Arterial Blood Gases  
- **Pao2**: Partial Pressure Of Oxygen  
- **Fio2**: Fraction Of Inspired Oxygen
### Table 2.:

**Cohort stratified by COVID status, Analysis for 2020 only.**

| VARIABLE | LEVEL | NEGATIVE \((N=119)\) | POSITIVE \((N=198)\) | \(P\)-VALUE |
|----------|-------|-----------------------|----------------------|-------------|
| **Age**  | median [iqr] | 55 [44, 65] | 58 [49, 66] | 0.0454785 |
| **Sex**  | Female | 39 (32.8) | 55 (27.8) | 0.4145237 |
|          | Male   | 80 (67.2) | 143 (72.2) | 0.0003173 |
| **ETHNICITY** | Black | 6 (5.9) | 13 (7.8) | 0.0003173 |
|          | White  | 79 (78.2) | 91 (54.5) | 0.0003173 |
|          | Asian  | 16 (15.8) | 63 (37.7) | 0.0003173 |
|          | missing | 18 | 31 | 0.0003173 |
| **IMD_QUINT** | Q1 | 55 (47.4) | 106 (53.8) | 0.0003173 |
|          | Q3 | 20 (17.2) | 26 (13.2) | 0.0003173 |
|          | Q5 | 12 (10.3) | 16 (8.1) | 0.0003173 |
|          | Q2 | 16 (13.8) | 28 (14.2) | 0.0003173 |
|          | Q4 | 13 (11.2) | 21 (10.7) | 0.0003173 |
|          | missing | 3 | 1 | 0.0003173 |
| **Height** | median [iqr] | 170.5 [164.2, 178.0] | 170 [163, 178] | 0.9231268 |
| **Weight** | missing | 13 | 37 | |
| | median [iqr] | 80 [70.0, 90.8] | 85 [74, 98] | 0.0229065 |
| | missing | 14 | 37 | |
| **Body mass index** | median [iqr] | 27.1 [24.2, 30.7] | 28.3 [25.9, 32.7] | 0.0113599 |
| | missing | 14 | 37 | |
| **Death** | No | 87 (73.1) | 125 (63.1) | |
| | Yes | 32 (26.9) | 73 (36.9) | 0.0882851 |
| **IHD** | No | 109 (91.6) | 178 (89.9) | |
| | Yes | 10 (8.4) | 20 (10.1) | 0.7627410 |
| **Atrial fibrillation (AF)** | No | 109 (91.6) | 186 (93.9) | |
| | Yes | 10 (8.4) | 12 (6.1) | 0.5710131 |
| **CCF** | No | 112 (94.1) | 197 (99.5) | |
| | Yes | 7 (5.9) | 1 (0.5) | 0.0097086 |
| **VTE** | No | 109 (91.6) | 191 (96.5) | |
| | Yes | 10 (8.4) | 7 (3.5) | 0.1083799 |
| **Hypertension** | No | 81 (68.1) | 108 (54.5) | |
| | Yes | 38 (31.9) | 90 (45.5) | 0.0239626 |
| **CVA** | No | 109 (91.6) | 191 (96.5) | |
| | Yes | 10 (8.4) | 7 (3.5) | 0.1083799 |
| Condition          | No            | Yes          | p-value   |
|--------------------|---------------|--------------|-----------|
| Diabetes mellitus  | 97 (81.5)     | 134 (67.7)   | 0.0106999 |
| CID                | 100 (84.0)    | 171 (86.4)   |           |
| Malignancy         | 101 (84.9)    | 180 (90.9)   |           |
| Not confirmed      | 4 (3.4)       | 4 (2.0)      |           |
| APA                | 95 (84.1)     | 162 (85.7)   |           |
| DOAC               | 100 (88.5)    | 176 (93.1)   |           |
| Warfarin           | 106 (93.8)    | 186 (98.4)   |           |
| Statin             | 83 (73.5)     | 129 (68.3)   |           |

- Diabetes mellitus: **Yes** vs. **No**
- CID: **Yes** vs. **No**
- Malignancy: **Yes** vs. **No**
- Not confirmed: **Yes** vs. **No**
- APA: **Yes** vs. **No**
- DOAC: **Yes** vs. **No**
- Warfarin: **Yes** vs. **No**
- Statin: **Yes** vs. **No**
| Variable                          | Yes       | No        | p-value |
|----------------------------------|-----------|-----------|---------|
| **ACE**                          | 30 (26.5) | 60 (31.7) | 0.4090385 |
| missing                          | 6         | 9         |         |
| **Beta blocker**                 | 97 (85.8) | 142 (75.1)|         |
| Yes                              | 16 (14.2) | 47 (24.9) | 0.0384546 |
| missing                          | 6         | 9         |         |
| **Surgical group**               | 70 (58.8) | 24 (12.1) | < 0.0001 |
| Yes                              | 49 (41.2) | 174 (87.9)|         |
| **Haematocrit**                  | median [iqr] | 0.4 [0.3, 0.4] | 0.4 [0.3, 0.4] | 0.2066641 |
| missing                          | 2         | 5         |         |
| **Platelet**                     | median [iqr] | 243 [163, 316] | 242 [180, 323] | 0.3215948 |
| missing                          | 0         | 1         |         |
| **Activated partial thromboplastin time** | median [iqr] | 30.4 [27.4, 33.4] | 30.4 [27.4, 33.4] | 0.2827159 |
| missing                          | 1         | 4         |         |
| **Prothrombin time**             | median [iqr] | 13.2 [12.0, 14.4] | 14.4 [13.2, 15.6] | 0.0001996 |
| missing                          | 0         | 1         |         |
| **D-dimer**                      | median [iqr] | 947 [535.8, 5,931.2] | 849 [438.0, 3,472.5] | 0.5888318 |
| missing                          | 77        | 51        |         |
|                  | median [iqr] |       |       |          |          |
|------------------|--------------|-------|-------|----------|----------|
| **Ferritin**     | 413 [154.5, 939.0] | 992 [428.0, 1,963.5] | 0.0023882 |
| missing          | 87           | 95    |       |          |          |
| **Fibrinogen**   | 4.2 [2.7, 5.0] | 5.2 [4.3, 5.9] | < 0.0001 |
| missing          | 60           | 92    |       |          |          |
| **Neutrophils**  | 9.1 [5.4, 12.1] | 8.2 [6.0, 11.4] | 0.4857807 |
| missing          | 0            | 3     |       |          |          |
| **Lymph**        | 1.3 [0.8, 2.2] | 0.9 [0.6, 1.3] | < 0.0001 |
| missing          | 1            | 4     |       |          |          |
| **Creatinine**   | 79 [64.5, 108.5] | 81 [62, 116] | 0.9003825 |
| missing          | 0            | 1     |       |          |          |
| **Urea**         | 5.7 [4.1, 9.0] | 6.3 [4.5, 10.2] | 0.2059393 |
| missing          | 1            | 1     |       |          |          |
| **RRT_group**    | No           | 102 (85.7) | 146 (74.1) |          |          |
| Yes              | 17 (14.3)    | 51 (25.9) | 0.0219907 |
| missing          | 0            | 1     |       |          |          |
| **ABG lactate**  | 1.6 [1.1, 2.7] | 1.4 [1.1, 1.9] | 0.0261479 |
| missing          | 1            | 1     |       |          |          |
| **ABG Pa02**     | 13.8 [9.2, 22.2] | 9.7 [8, 12] | < 0.0001 |
| missing          | 1            | 2     |       |          |          |
| **ABG fio2**     | 0.3 [0.2, 0.5] | 0.6 [0.2, 0.8] | < 0.0001 |
| missing          | 1            | 2     |       |          |          |
| Category                          | Yes     | No     | Abbreviation                                      | p-value            |
|----------------------------------|---------|--------|--------------------------------------------------|-------------------|
| **VTE prophylaxis group**        | 105 (89.7) | 12 (10.3) | Yes                                               | 0.0304708         |
|                                  | 190 (96.4) | 7 (3.6)  | No                                               |                   |
|                                  | 2        | 1      | Missing                                          |                   |
| **Arterial event group**         | 110 (92.4) | 9 (7.6)  | No                                               | 0.9123990         |
|                                  | 181 (91.4) | 17 (8.6) | Yes                                              |                   |
| **DVT group**                    | 114 (95.8) | 5 (4.2)  | No                                               | 0.3381037         |
|                                  | 183 (92.4) | 15 (7.6) | Yes                                              |                   |
| **Pulmonary embolism group**     | 114 (95.8) | 5 (4.2)  | No                                               | 0.0064762         |
|                                  | 169 (85.4) | 29 (14.6)| Yes                                              |                   |
| **Arteriovenous access thrombosis group** | 115 (96.6) | 4 (3.4)  | No                                               | 0.4911531         |
|                                  | 195 (98.5) | 3 (1.5)  | Yes                                              |                   |
| **Event**                        | 99 (83.2) | 20 (16.8)| No                                               | 0.0366960         |
|                                  | 143 (72.2)| 55 (27.8)| Yes                                              |                   |

**Abbreviations**:  
IHD: Ischemic Heart Disease, IMD_Quint: Index Of Multiple Deprivation Quintiles,  
CCF: Congestive Cardiac Failure, VTE: Venous Thromboembolism, DOAC: Direct Oral Anticoagulant,  
APA: Antiplatelet Agents, BB: Beta Blocker, CVA: Cerebrovascular Accident, CLD: Chronic Lung Disease, ACE: Angiotensin-Converting Enzyme Inhibitors, RRT: Renal Replacement Therapy, ABG: Arterial Blood Gases, Pao2: Partial Pressure Of Oxygen, Fio2: Fraction Of Inspired Oxygen
| EVENT: OR (95% CI, p-value)         |   |
|------------------------------------|---|
| VTE                               | Yes | 14.00 (3.98-54.34, p<0.001) |
| RRT_GRP                           | Yes | 2.40 (1.21-4.72, p=0.011)   |
| DOAC                              | Yes | 1.36 (0.43-3.98, p=0.584)   |
| COVID19StatusGRP                  | Positive | 2.64 (1.29-5.77, p=0.011) |
| APA                               | Yes | 0.25 (0.07-0.71, p=0.018)   |
| Lymph                             | -   | 0.88 (0.57-1.02, p=0.525)   |
| PT                                | -   | 0.98 (0.91-1.05, p=0.623)   |
| APTT                              | -   | 1.01 (0.98-1.04, p=0.454)   |
| ABGLac                            | -   | 1.17 (1.03-1.33, p=0.013)   |
| AGE                               | -   | 1.01 (0.99-1.04, p=0.268)   |

OR, 95% CI
EVENT: OR (95% CI, p-value)

AGE
- 1.03 (1.01-1.06, p=0.015)

APA
Yes 0.26 (0.06-0.81, p=0.037)
Figure Legends

Figure 1: Multi-variate analysis for composite outcome (EVENTS). The analysis includes only patients from April 2020.

Figure 2: Multi-variate analysis for composite outcome (EVENTS). The analysis includes only COVID-positive patients from April 2020.
Declaration of interest

The named authors have no conflict of interest, financial or otherwise.

Sincerely,

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