Low Incidence of Venous Thrombosis But High Incidence of Arterial Thrombotic Complications Among Critically Ill COVID-19 Patients in Singapore

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Abstract

Background: Arterial and venous thrombosis are reported to be common in critically ill COVID-19 patients.

Method and Results: This is a national multicenter retrospective observational study involving all consecutive adult COVID-19 patients who required intensive care units (ICU) admission between 23 January 2020 and 30 April 2020 in Singapore. 111 patients were included and the venous and arterial thrombotic rates in ICU were 1.8% (n=2) and 9.9% (n=11), respectively. Major bleeding rate was 14.8% (n=16).

Conclusions: Critically ill COVID-19 patients in Singapore have lower venous thromboembolism but higher arterial thrombosis rates and bleeding manifestations than other reported cohorts.

Introduction

COVID-19 is associated with hypercoagulability[1] and a high incidence of thrombotic complications in critically ill patients[2]. Initial reports in Western populations suggest thrombotic rates as high as 49% despite thromboprophylaxis[3] while deep vein thrombosis (DVT) rate of 46% have been reported by the Chinese[4]. These disconcerting findings have prompted suggestion for empiric escalation of prophylactic anticoagulation therapy[3] but expert consensus[5, 6] and more recent data have questioned this rationale[7]. Of concern is hypercoagulability overlapping with sepsis-induced coagulopathy and thrombotic microangiopathy, resulting in a dynamic haemostatic environment with higher potential for bleeding complications from interaction with pharmacological thromboprophylaxis. Accurate profiling of thrombotic and bleeding complications in these patients is paramount for optimal case management and outcomes.

This study describes the thrombotic and bleeding manifestations among critically ill COVID-19 patients in Singapore.

Methods

This multi-center retrospective cohort study involved all eight public general hospitals with intensive care units (ICU) in Singapore-Alexandra Hospital (AH), Changi General Hospital, Khoo Teck Puat Hospital, National University Hospital, Ng Teng Fong General Hospital, Tan Tock Seng Hospital/National Centre for Infectious Disease campus, Sengkang General Hospital and Singapore General Hospital. From 23 January 2020 through 30 April 2020, all adult patients with COVID-19 confirmed by a respiratory SARS-CoV2 RT-PCR test and were admitted to any of the ICUs were identified. The study protocol was approved by the centralized institutional review board covering all participating hospitals (protocol no. CIRB 2020-2528) except AH which only contributed data on the total number of COVID-19 ICU admission and thrombotic events. Anonymized data was provided by each participating site and pooled for analyses. The primary outcome was any venous or arterial thrombotic event in the ICU. Other measures included (1) any thrombotic events throughout the period of hospitalisation, (2) major and minor bleeding events
during hospitalisation, (3) factors associated with thrombotic and bleeding outcomes and (4) mortality. Venous thromboembolism (VTE) was diagnosed based on clinical suspicion and confirmation by Doppler ultrasound of the extremities or computed tomography. Arterial events such as myocardial infarction (MI) and ischaemic stroke were confirmed by relevant investigations and verified by attending specialists. Bleeding complications were graded using the modified World Health Organization (WHO) grading system.

Descriptive statistics were used to analyse continuous and categorical variables. Logistic regression was used to evaluate potential risk factors for the secondary outcomes. All data analyses were performed using SPSS version 23.0 (IBM, USA).

Results

111 COVID-19 patients were admitted to the ICUs during the study period. The overall thrombotic rates in ICU were 11.7% (95% confidence interval (CI): 7.0–19.0%) (n=13) with 1.8% (95% CI: 0.5–6.3%) (n=2) venous and 9.9% (95% CI: 5.6–16.9%) (n=11) arterial events. Corresponding rates throughout hospitalisation, censored at 30 April 2020, were 18.0% (95% CI: 12.0–26.2%) (n=20) with 6.3% (95% CI: 3.1–12.5%) (n=7) venous and 11.7% (95% CI: 7.0–19.0%) (n=13) arterial events. After the exclusion of cases from AH (n=3, no thrombotic events), the remaining 108 patients contributed a total of 311.4 patient-weeks for further analysis (Table 1). As of 30 April, 70 patients (64.8%) had been discharged while 9 had died (8%) and 30 (27.7%) were still hospitalized.

Two VTE events, comprising a lower limb DVT and a line-related upper limb DVT, were diagnosed in two patients in ICU, giving a VTE rate of 0.6 (95% CI: 0.1–2.3) per 100-person-weeks. For the entire duration of hospitalization, the cumulative VTE rate rose to 2.2 (95% CI: 0.9–4.6) per 100-patient-weeks. Of these, the majority were pulmonary embolism (Table 2). 75% of the patients received therapeutic anticoagulation after the diagnosis of VTE with 2 subsequently stopped due to bleeding complications.

The arterial thrombosis rate during ICU stay was 3.5 (95% CI: 1.8–6.3) per 100-patient-weeks. This increased marginally during the entire hospitalization to 4.2 (95% CI: 2.2–7.1) per 100-patient-weeks. These events were mainly MI of which one was fatal (Table 2).

The overall thrombotic complication rate in these 108 patients was 6.4 (95% CI: 3.9–9.9) per 100-patient-weeks. 46.2% patients were receiving pharmacological thromboprophylaxis at the time of the events.

The major bleeding (WHO grade 3-4) rate was 5.1 (95% CI: 2.9–8.3) per 100-patient-week. (Table 2) with an overall bleeding rate was 6.4 (95% CI: 3.9–9.9) per 100-patient-days. One bleeding event, from an intracranial hemorrhage, was fatal.

Whilst no clinical factor was significantly associated with the occurrence of thrombotic events, the need of haemodialysis support in ICU and higher fibrinogen level were respectively associated with higher and
lower risk for major bleeding events (Table 3a). Mortality was associated with thrombosis but not bleeding (Table 3b).

**Discussion**

Although only two-thirds of our critically ill COVID-19 patients received thromboprophylaxis, the incidence rate of VTE was only 1.8%. This rate is far lower than similar published studies that included only objectively confirmed VTE events[3, 8]. Several reasons could account for the lower VTE rates in our report. Previous studies have shown patients of Asian-descent have lower risk for VTE compared to Western cohorts[9]. Our patients were also younger with fewer comorbidities and they tended to present to the hospital earlier in their course of illness[4,8], which might have led to earlier interventions as reflected in the low median APACHE and SOFA scores on transfer to ICU.

Of interest, the occurrence of further VTE events after ICU stay suggest the persistence of hypercoagulability[10]. Thromboprophylaxis measures hence should be continued for these patients throughout hospitalisation. However, a more intensified anticoagulation strategy for our patients was negated by the 14.8% major bleeding rate observed, which was considerably higher than other cohorts[7]. This finding is consistent with previous reports of higher bleeding rates among Asian patients taking warfarin for atrial fibrillation, compared with non-Asians counterparts[11].

In contrast to VTE, our arterial event rates are high with mainly MIs occurring almost exclusively in the ICU, when the patients were the sickest. Unlike VTE, comparative arterial thrombotic rates in other COVID-19 cohorts are lower at 4%[3, 7] with mainly strokes rather than MIs. Myocardial injury in up to 30% of COVID-19 patients have been reported by some Chinese investigators but this was based on elevation of cardiac troponin levels[12] without verification of MI. Apart from ethnic differences, the baseline cardiovascular risk factors of our patients did not differ notably from existing literature[7] and thus the precise reason behind the higher rates seen in our population is not apparent currently.

This study is limited by its retrospective nature as with most other studies conducted under the present pandemic environment. There was no established imaging protocol for suspected VTE consistent across the hospitals. Similarly, clinical and laboratory data was not uniformly collected and trivial bleeds might have been missed. The small number of thrombotic and bleeding events also limited our statistical analysis of inference.

Nonetheless, we believe our data is adequately robust to highlight the differences in thrombosis presentations and higher bleeding manifestations compared to other published cohorts. Our findings thus argue against the need for intensification of pharmacological thromboprophylaxis in similar Asian-predominant populations. Use of global coagulation assays[13] in critically ill COVID-19 patients to guide thromboprophylaxis warrant future consideration and exploration. Extended thromboprophylaxis during hospitalisation should also be considered. The role of antiplatelets and low dose direct anti-Xa inhibitors as cardio-protectants should be among future investigations.
Declarations

Ethics approval and consent to participate

Ethics approval for this multicentre study was obtained from the SingHealth Centralised Institution Review Board.

Data Availability:

For original data, please contact eng_soo_yap@nuh.edu.sg.

Competing Interests:

The authors do not declare any competing interests.

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This multicentre study was performed without any funding received.

Authors’ contribution:

CWT, BEF and ESY initiated and designed the study and had full access to all the study data and take full responsibility for the integrity of the data and accuracy of the data analysis. HJN initiated and critically revised the manuscript. WT collected and analysed the data and contributed to the writing of the manuscript. CYL and LHL critically revised the manuscript. MLT, HS, D, SZ, WMP, SSWC, VCLC, CAG, CCRC, LML, JYT, KCHL, GCP, JGHL, VKH contributed to data acquisition and interpretation. All authors reviewed and approved the final version of the manuscript.

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References

1. Iba T, Levy JH, Levi M, Connors JM, Thachil J: Coagulopathy of Coronavirus Disease 2019. *Crit Care Med* 2020.
2. Al-Ani F, Chehade S, Lazo-Langner A: Thrombosis risk associated with COVID-19 infection. A scoping review. *Thromb Res* 2020, 192:152-160.
3. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H: Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res* 2020, 191:148-150.
4. Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, Zhang C, Li H, Xia X, Kong S, et al: Deep Vein Thrombosis in Hospitalized Patients with Coronavirus Disease 2019 (COVID-19) in Wuhan, China: Prevalence, Risk Factors, and Outcome. Circulation 2020.

5. Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, Holley AB, Jimenez D, LeGal G, Rali P, Wells P: Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST Guideline and Expert Panel Report. Chest 2020.

6. Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, Levi M, Samama CM, Thachil J, Giannis D, et al: Scientific and Standardization Committee Communication: Clinical Guidance on the Diagnosis, Prevention and Treatment of Venous Thromboembolism in Hospitalized Patients with COVID-19. J Thromb Haemost 2020.

7. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JC, Fogerty AE, Waheed A, Goodarzi K, Bendapudi P, Bornikova L, Gupta S, et al: COVID and Coagulation: Bleeding and Thrombotic Manifestations of SARS-CoV2 Infection. Blood 2020.

8. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Muller MCA, Bouman CCS, Beenen LFM, Kootte RS, Heijmans J, et al: Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020.

9. Lee LH, Gallus A, Jindal R, Wang C, Wu CC: Incidence of Venous Thromboembolism in Asian Populations: A Systematic Review. Thromb Haemost 2017, 117:2243-2260.

10. Pavoni V, Gianesello L, Pazzi M, Stera C, Meconi T, Frigieri FC: Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. J Thromb Thrombolysis 2020.

11. Chiang CE, Wang KL, Lip GY: Stroke prevention in atrial fibrillation: an Asian perspective. Thromb Haemost 2014, 111:789-797.

12. Bonow RO, Fonarow GC, O’Gara PT, Yancy CW: Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. JAMA Cardiol 2020.

13. Mortus JR, Manek SE, Brubaker LS, Loor M, Cruz MA, Trautner BW, Rosengart TK: Thromboelastographic Results and Hypercoagulability Syndrome in Patients With Coronavirus Disease 2019 Who Are Critically Ill. JAMA Netw Open 2020, 3:e2011192.

Tables

Table 1. Clinical characteristics and laboratory findings of 108 critically ill COVID-19 patients stratified according to their thrombosis status.
| Characteristics                          | All patients (n=108) | No thrombotic events (n=88) | Venous thrombosis (n=7) | Arterial thrombosis (n=13) |
|----------------------------------------|----------------------|-----------------------------|-------------------------|---------------------------|
| **Demographics**                       |                      |                             |                         |                           |
| Age (years)                            | 62 (19-88)           | 61.5 (19-88)                | 62 (54-75)              | 64 (40-82)                |
| Male                                   | 75 (69.4%)           | 59 (67%)                    | 5 (71.4%)               | 11 (84.6%)                |
| Body weight >100kg                     | 6 (5.6%)             | 5 (5.7%)                    | 0 (0%)                  | 1 (7.7%)                  |
| Ethnicity                              |                      |                             |                         |                           |
| Chinese                                | 67 (62%)             | 55 (62.5%)                  | 6 (85.7%)               | 6 (46.2%)                 |
| Malay                                  | 14 (13%)             | 12 (13.6%)                  | 1 (14.3%)               | 1 (7.7%)                  |
| Indian                                 | 16 (14.8%)           | 12 (13.6%)                  | 0 (0%)                  | 4 (30.8%)                 |
| Thai/Burmese                           | 3 (2.8%)             | 3 (3.4%)                    | 0 (0%)                  | 0 (0%)                    |
| Others                                 | 8 (7.4%)             | 6 (6.8%)                    | 0 (0%)                  | 2 (15.4%)                 |
| **Pre-existing medical conditions**    |                      |                             |                         |                           |
| Major illness                          |                      |                             |                         |                           |
| Hypertension                           | 62 (57.4%)           | 50 (56.8%)                  | 3 (42.9%)               | 9 (69.2%)                 |
| Ischaemic heart disease                | 21 (19.4%)           | 16 (18.2%)                  | 2 (28.6%)               | 3 (23.1%)                 |
| Dyslipidemia                           | 52 (48.1%)           | 40 (45.5%)                  | 4 (57.1%)               | 8 (61.5%)                 |
| Heart failure                          | 4 (3.7%)             | 4 (4.5%)                    | 0 (0%)                  | 0 (0%)                    |
| Previous stroke                        | 6 (5.6%)             | 5 (5.7%)                    | 0 (0%)                  | 1 (7.7%)                  |
| Diabetes                               | 40 (37%)             | 35 (39.8%)                  | 1 (14.3%)               | 4 (30.8%)                 |
| Renal impairment                       | 15 (13.9%)           | 12 (13.6%)                  | 1 (14.3%)               | 2 (15.4%)                 |
| History of venous thromboembolism      | 4 (3.7%)             | 4 (4.5%)                    | 0 (0%)                  | 0 (0%)                    |
| Anti-coagulant therapy at admission    | 4 (3.7%)             | 4 (4.5%)                    | 0 (0%)                  | 0 (0%)                    |
| Anti-platelet agent at admission       | 20 (17%)             | 15 (17%)                    | 2 (28.6%)               | 3 (23.1%)                 |
### ICU-specific findings

|                      | Median     | Range       | Median     | Range       | Median     | Range       |
|----------------------|------------|-------------|------------|-------------|------------|-------------|
| APACHE II            | 11 (0-32)  | 10.5 (0-32) | 11 (6-27)  | 11 (4-20)   |
| SOFA                 | 3 (0-16)   | 3 (0-12)    | 2 (0-16)   | 4 (1-9)     |
| Mechanical ventilation | 84 (77.8%) | 66 (75%)    | 5 (71.4%)  | 13 (100%)   |
| Dialysis support     | 28 (25.9%) | 21 (23.9%)  | 2 (28.6%)  | 5 (38.5%)   |
| Onset of symptoms till ICU admission in days | 8 (0-34) | 7.5 (0-34) | 8 (4-15) | 9 (3-34) |
| Prophylactic anticoagulation | 69 (63.9%) | 59 (67%) | 4 (57.1%) | 6 (46.2%) |

### Thrombosis-related features

|                                | Median     | Range       | Median     | Range       |
|--------------------------------|------------|-------------|------------|-------------|
| Onset of thrombosis from hospital admission in days | 13 (7-42) | 7 (0-25)    |            |             |
| Onset of thrombosis from admission to ICU in days | 7 (2-23)  | 5 (0-13)    |            |             |

### Bleeding complications

|                                | Median     | Range       | Median     | Range       | Median     | Range       |
|--------------------------------|------------|-------------|------------|-------------|------------|-------------|
| Major bleeding events          | 16 (14.8%) | 10 (11.4%)  | 3 (42.9%)  | 3 (23.1%)   |
| Minor bleeding events          | 4 (3.7%)   | 4 (4.5%)    | 0 (0%)     | 0 (0%)      |
| Death                          | 9 (8.3%)   | 5 (5.7%)    | 1 (14.3%)  | 3 (23.1%)   |

### Laboratory findings, median (range)

|                                | Median     | Range       | Median     | Range       | Median     | Range       |
|--------------------------------|------------|-------------|------------|-------------|------------|-------------|
| PT (s)                         | 12.6 (11.2-13.6) | 12.0 (11.0-13.1) | 13.4 (13.2-15.3) | 12.8 (11.5-15.7) |
| aPTT (s)                       | 36.9 (32.8-41.9) | 36.8 (32.6-41.2) | 33.8 (32.6-38.2) | (39.8 (32.9-42.2) |
| D-dimer (mg/L FEU)             | 2.3 (1.2-6.1) | 1.9 (1.2-5.5) | 2.7 (2.4-2.7) | 6.1 (1.8-12.8) |
| Fibrinogen (g/L)               | 5.9 (4.2-8.2) | 6.8 (4.1-8.0) | 4.0 (2.1-5.6) | 6.2 (4.7-9.2) |
| White blood count (x10^9 /L)   | 8.5 (6.1-11.7) | 8.3 (6.0-11.1) | 11.3 (6.5-14.9) | 10.5 (7.5-12.9) |
| Continuous variables denoted as median (range); categorical variables as number (%) |
| Absolute lymphocyte count (x10^9 /L) | 0.9 (0.6-1.5) | 0.9 (0.6-1.5) | 0.9 (0.6-1.5) | 0.9 (0.6-1.7) |
| Absolute neutrophil count (x10^9 /L) | 7.1 (4.5-10.3) | 6.9 (4.5-10.1) | 7.9 (5.2-13.8) | 8.6 (5.0-11.5) |
| Plaletet count (x10^9 /L) | 221 (116-350) | 219 (161-350) | 232 (155-385) | 230 (160-338) |
| CRP (mg/L) | 158 (99-249) | 174 (97-265) | 142 (17-198) | 140 (114-163) |
| Procalcitonin (µg/L) | 0.5 (0.2-1.3) | 0.5 (0.2-1.3) | 0.2 (0.2-2.3) | 0.6 (0.2-2.1) |
| Creatinine (µmol/L) | 85 (68-120) | 85 (68-120) | 78 (62-135) | 88 (71-120) |

**Table 2. Description of the thrombotic and bleeding cases.**
| Type of event                              | Number of cases | Details |
|-------------------------------------------|-----------------|---------|
| Pulmonary embolism (PE) only              | 4               | 4 cases of PE diagnosed on CTPA |
| PE and proximal lower limb deep vein thrombosis (DVT) | 1 | 1 case had both PE and DVT |
| Proximal lower limb DVT only              | 1               | 1 case had both proximal lower limb DVT |
| Other venous thromboembolism sites        | 1               | 1 case had line related upper limb DVT |
| Myocardial infarction (MI) only           | 11              | 11 cases had MI |
| MI and ischaemic stroke                   | 1               | 1 case had both MI and ischaemic stroke |
| Ischaemic stroke                          | 1               | 1 case had ischaemic stroke |
| Bleeding (Major)                          | 16              | Intracranial haemorrhage – while on IV prophylactic heparin for CVA |
|                                           |                 | 2 cases of intracranial haemorrhage – while on ECMO with IV unfractionated Heparin |
|                                           |                 | PR bleeding from haemorrhoids/anal fissures – while on therapeutic LMWH for PE |
|                                           |                 | PR bleeding from haemorrhoids – while on prophylactic LMWH |
|                                           |                 | PR bleed from haemorrhoids – not on anticoagulation |
|                                           |                 | Severe gastritis with melena – while on S/C therapeutic LMWH for DVT |
|                                           |                 | Recurrent Forrest 2C ulcer bleed – while on S/C therapeutic LMWH for DVT |
|                                           |                 | Stress gastropathy with nasogastric tube erosion and worsening anaemia – not on anticoagulation |
|                                           |                 | Coffee ground NG aspirate related to celecoxib use |
|                                           |                 | Coffee ground NG aspirate – not on any anticoagulation |
|                                           |                 | Gastrointestinal bleed – not on any anticoagulation |
|                                           |                 | Haemorrhagic encephalitis and PR bleed – while on prophylactic LMWH |
|                                           |                 | Haemoptysis – while on prophylactic LMWH |
|                                           |                 | Bloody trachea aspirates – while on IV unfractionated |
### Heparin for STEMI

|                          |                                                                 |
|--------------------------|-----------------------------------------------------------------|
| **Bleeding (Minor)**     | 4 cases of blood stained sputum – while on prophylactic LMWH   |
| **Mild haematuria**      | after urinary catheter insertion – while on apixaban prophylaxis|
| **Mild bleeding**        | from central venous catheter – while on prophylactic LMWH       |

Note: acute pulmonary embolism was diagnosed with CT-pulmonary angiography, deep vein thrombosis/upper extremity vein thrombosis was diagnosed with ultrasonography, strokes were diagnosed with CT.

CT – computed topography; ECMO – Extracorporeal membrane oxygenation; IV – intravenous; LMWH – Low molecular weight heparin; NG Aspirate – Nasogastric aspirate; S/C – subcutaneous; STEMI – ST Elevation MI.

Table 3. (a) Odds ratio of clinical and laboratory factors for thrombotic (arterial and venous) and major bleeding events. (b) Association of thrombotic and major bleeding events to mortality.
## a) Factors

|                          | Thrombotic Events | Major Bleeding Events |
|--------------------------|-------------------|-----------------------|
|                          | Odds Ratio | 95% Confidence Interval | P value | Odds Ratio | 95% Confidence Interval | P value |
|                          |           | Lower Bound | Upper Bound |       |           | Lower Bound | Upper Bound |       |
| **Baseline demographics**|           |             |             |       |           |             |             |       |
| Age                      | 1.034     | .990        | 1.080       | .13  | 1.026     | .980        | 1.075       | .27  |
| Gender, male             | 1.966     | .603        | 6.414       | .26  | 1.381     | .410        | 4.650       | .60  |
| Ethnicity, Chinese       | .900      | .333        | 2.430       | .84  | .754      | .257        | 2.207       | .61  |
| Diabetes                 | .505      | .168        | 1.514       | .22  | .740      | .237        | 2.310       | .60  |
| Hypertension             | 1.140     | .424        | 3.065       | .80  | .704      | .243        | 2.040       | .52  |
| Hyperlipidemia           | 1.800     | .670        | 4.835       | .24  | 1.091     | .377        | 3.155       | .87  |
| Renal impairment         | 1.118     | .284        | 4.399       | .87  | 2.455     | .672        | 8.962       | .17  |
| Pre-existing cardiovascular disease* | 1.667 | .562 | 4.945 | .36 | .780 | .203 | 2.999 | .72 |
| **ICU-specific features**|           |             |             |       |           |             |             |       |
| APAHCE score             | .979      | .904        | 1.061       | .61  | .997      | .918        | 1.082       | .94  |
| SOFA score               | 1.043     | .890        | 1.224       | .60  | 1.161     | .993        | 1.358       | .06  |
| Mechanical ventilation   | 3.000     | .644        | 13.973      | .16  | 5.000     | .626        | 39.963      | .13  |
| Dialysis support         | 1.718     | .606        | 4.867       | .31  | 4.940     | 1.629       | 14.978      | .005 |
| Use of thromboprophylaxis| .492      | .184        | 1.313       | .16  | .376      | .128        | 1.108       | .08  |
| **Laboratory findings**  |           |             |             |       |           |             |             |       |
| PT                       | 1.133     | .965        | 1.329       | .13  | 1.060     | .906        | 1.241       | .47  |
| aPTT                     | .999      | .967        | 1.032       | .97  | 1.003     | .967        | 1.041       | .88  |
| D-dimer                  | 1.030     | .929        | 1.143       | .57  | .783      | .454        | 1.352       | .38  |
| Fibrinogen               | .956      | .751        | 1.217       | .78  | .658      | .453        | .957        | .03  |
| White blood count        | 1.037     | .962        | 1.117       | .35  | .994      | .906        | 1.089       | .89  |
| Absolute lymphocyte count| 1.246     | .698        | 2.226       | .46  | .573      | .217        | 1.511       | .26  |
|                                | 1.030 | .945 | 1.123 | .50  | 1.001 | .905 | 1.107 | .99  |
|--------------------------------|-------|------|-------|------|-------|------|-------|------|
| Absolute neutrophils count     |       |      |       |      |       |      |       |      |
| Platelet count                 | .999  | .996 | 1.002 | .60  | .998  | .995 | 1.002 | .35  |
| C-reactive protein             | .995  | .989 | 1.001 | .09  | 1.001 | .995 | 1.006 | .75  |
| Procalcitonin                  | .996  | .969 | 1.023 | .76  | .937  | .776 | 1.132 | .50  |
| Creatinine                     | 1.000 | .996 | 1.004 | .86  | .999  | .995 | 1.004 | .78  |
| b) Factors                     |       |      |       |      |       |      |       |      |
| Mortality                      |       |      |       |      |       |      |       |      |
| Thrombotic events              | 4.150 | 1.004| 17.161| .05  |       |      |       |      |
| Arterial events                | 4.450 | .961 | 20.599| .06  |       |      |       |      |
| Venous events                  | 1.937 | .207 | 18.141| .56  |       |      |       |      |
| Major bleeding events          | 3.308 | .735 | 14.878| .12  |       |      |       |      |

* Included ischemic heart disease, congestion heart failure and stroke.