Abstract

Objectives: This study aimed to investigate in-hospital mortality rates in patients with coronavirus disease (COVID-19) according to enoxaparin and heparin use.

Methods: This retrospective cohort study included 962 patients admitted to two hospitals in Kuwait with a confirmed diagnosis of COVID-19. Cumulative all-cause mortality rate was the primary outcome.

Results: A total of 302 patients (males, 196 [64.9%]; mean age, 57.2 ± 14.6 years; mean body mass index, 29.8 ± 6.5 kg/m²) received anticoagulation therapy. Patients receiving anticoagulation treatment tended to have pneumonia (n = 275 [91.1%]) or acute respiratory distress syndrome (n = 106 [35.1%]), and high D-dimer levels (median [interquartile range]: 608 [523;707] ng/mL). The mortality rate in this group was high (n = 63 [20.9%]). Multivariable logistic regression, the Cox proportional hazards, and Kaplan-Meier models revealed that the use of therapeutic anticoagulation agents affected the risk of all-cause cumulative mortality.

Conclusion: Age, hypertension, pneumonia, therapeutic anticoagulation, and methylprednisolone use were found to be strong predictors of in-hospital mortality. In elderly hypertensive COVID-19 patients on therapeutic anticoagulation were found to have 2.3 times higher risk of in-hospital mortality. All cause in-hospital mortality rate in the therapeutic anticoagulation group was up to 21%.

Keywords
anticoagulation, SARS-CoV-2, in-hospital mortality, COVID-19, pneumonia

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**Introduction**

The hypercoagulable state and associated risk of thrombotic complications is common in critically ill severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients. Prophylactic use of therapeutic anticoagulation agents reduces the risk of such complications. The incidence of such complications ranges from 18% to 37%. These complications are common in SARS-CoV-2 patients admitted to intensive care units (ICU). In these patients, the risk of venous thromboembolism has been estimated at 47%. Thrombosis has been reported as an independent predictor of mortality in SARS-CoV-2 patients. Some studies have suggested that the use of therapeutic anticoagulation agents may reduce the risk of mortality; however, the evidence remains inconclusive.

**Methods**

**Study Design and Procedure**

This retrospective cohort study included 962 patients with confirmed SARS-CoV-2 infection, both Kuwaitis and non-Kuwaitis, and aged ≥18 years (Figure 1). All data were extracted from electronic medical records from two hospitals in Kuwait: Jaber Al-Ahmed Hospital and Al Adan General Hospital. An electronic case record form was used for data entry.

SARS-CoV-2 infection was confirmed by a positive reverse transcription polymerase chain reaction analysis of a swab sample obtained from the nasopharynx. The care of all patients was standardized according to a protocol established by the Ministry of Health in Kuwait. The standing committee for coordination of health and medical research at the Ministry of Health in Kuwait waived the requirement for informed consent and approved the study protocol (institutional review board number 2020/1422).

**Definitions**

The primary outcome of interest was SARS-CoV-2-related mortality rate (ICD-10 code U07.1). Secondary outcomes of interest included admission to the ICU and hospitalization duration. Anticoagulation therapy was defined as the use of enoxaparin or unfractionated heparin in hospitalized coronavirus disease (COVID-19) patients. Patients who received anticoagulants were considered exposed to anticoagulation despite the duration of the therapy. The majority of patients were managed with a minimum dose of enoxaparin of 80 mg up to 200 mg per day. Local protocol of anticoagulation therapy in COVID-19 hospitalized patients, duration of therapy, and follow up of patients were beyond the scope of our study. Obstructive and restrictive lung diseases were clustered under the chronic lung disease category. Patients receiving immunosuppressive therapy were defined as immunocompromised patients.

According to the main study hospital, Jaber Alahmad hospital, complete blood count (CBC) parameters were analyzed by Sysmex, while D-dimer was examined by Stago machine. All biochemistry laboratory parameters were scanned by Beckman Coulter manufacture company machines, expect for procalcitonin and 25 (OH) vitamin D which were analyzed by Roche cobas analyzer. The following are the catalog numbers: CBC (CD-994-563, CV-377-552, CP-066-715, BU-306-227, 904-1131-7, 054-3351-4), Creatinine (OSR61204), LDH (OSR6128), CRP (447280), Procalcitonin (05056888003), D-dimer (00662), 25 (OH) vitamin D (05894913-190), Troponin I HS (B52699), Ferritin (33020), Creatinine kinase (OSR6X79), ALT (OSR6X07), AST (OSR6X09), ALP (OSR6X04), GGT (OSR6X20), Albumin (OSR6X02). Total bilirubin (OSR6X12), Direct bilirubin (OSR6X11). Oxygen requirements were divided into “high” and “low” categories. “High” oxygen requirement included the use of extracorporeal membrane oxygenation, invasive ventilation, non-invasive ventilation, and high-flow oxygen. Non-rebreather mask or nasal cannula patients were included in the “low” oxygen requirement category. The clinical and laboratory variables of interest included sociodemographic characteristics, body mass index (BMI), smoking status, sources of transmission, co-morbidities, clinical presentation, laboratory findings, medications received at hospital, and durations of the ICU and hospital admission.

**Statistical Analysis**

Frequencies, percentages, means ± standard deviations (SD) and medians ± interquartile ranges [IQR] are reported as descriptive statistics. The association between anticoagulation category (yes, no) and other variables was examined using the Pearson \( \chi^2 \) test. Logistic regression analysis was used to examine the effects of therapeutic anticoagulation agent use, age, hypertension, diabetes mellitus (DM), COVID-19 pneumonia, fever at presentation, and use of methylprednisolone on cumulative all-cause mortality rates. The Cox proportional hazards regression model and Kaplan-Meier method were used to estimate the impact of therapeutic anticoagulation agent use on mortality rates. Statistical analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Baseline Characteristics**

The patients’ baseline characteristics are presented in Table 1. In the group receiving anticoagulation treatment (n = 302; mean age, 57.2 ± 14.6 years; mean BMI, 29.8 ± 6.53 kg/m²), 132 (53.9%) and 99 (40.4%) patients had COVID-19 due to community and close contact transmission, respectively. The corresponding values for patients not receiving anticoagulation treatment (n = 660; mean age, 47.0 ± 15.4 years; mean BMI
28.6 ± 5.97 kg/m²), were 214 (34.8%) and 287 (46.7%), respectively. The prevalence rates of hypertension, DM, cardiovascular disease, and chronic kidney disease were higher in the anticoagulation group than in the non-anticoagulation group. COVID-19 pneumonia (n = 275 [91.1%]) and acute respiratory distress syndrome (n = 106 [35.1%]) were more common among patients receiving anticoagulation treatment than among those not receiving this treatment. In addition, 113 (37.4%) patients receiving anticoagulation treatment required an ICU admission, remaining in the hospital for an average of 18.0 [5.00; 60.0] days. The overall mortality rate was 9.04% (n = 87). The mortality rate was higher among patients receiving anticoagulation treatment (n = 63 [20.9%]) than among those not receiving this treatment (n = 24 [3.6%]).

**Signs and Symptoms**

Table 2 summarizes the clinical characteristics of COVID-19 patients at presentation, stratified by anticoagulation category. Patients receiving anticoagulation treatment presented with fever (n = 210 [69.5%]), dyspnea (n = 174 [57.6%]), dry cough (n = 167 [55.3%]), and sore throat (n = 19 [6.3%]).

**Laboratory Findings Stratified by Anticoagulation Therapy**

Patients receiving anticoagulation therapy had increased white blood cell and neutrophil counts, and creatinine,
Table 1. Baseline Characteristics of SARS-CoV-2 Patients, Stratified by Anticoagulation Therapy.

|                      | [ALL] N = 962 | Anticoagulation = no N = 660 | Anticoagulation = yes N = 302 | p-value | N |
|----------------------|--------------|------------------------------|-------------------------------|---------|---|
| Age, ± SD, years     | 50.2 (15.9)  | 47.0 (15.4)                  | 57.2 (14.6)                  | <0.001  | 962 |
| BMI, ± SD, kg/m²     | 29.0 (6.18)  | 28.6 (5.97)                  | 29.8 (6.53)                  | 0.033   | 606 |
| Male                 | 615 (64.1%)  | 419 (63.8%)                  | 196 (64.9%)                  | 0.791   | 959 |
| Smoking:             |              |                              |                              | 0.070   | 270 |
| Current Smoker       | 38 (14.1%)   | 29 (18.0%)                   | 9 (8.26%)                    |         |    |
| Ex-Smoker            | 28 (10.4%)   | 17 (10.6%)                   | 11 (10.1%)                   |         |    |
| Never Smoked         | 204 (75.6%)  | 115 (71.4%)                  | 89 (81.7%)                   |         |    |
| Source of transmission: |        |                              |                              | <0.001  | 860 |
| Community            | 346 (40.2%)  | 214 (34.8%)                  | 132 (53.9%)                  |         |    |
| Contact              | 386 (44.9%)  | 287 (46.7%)                  | 99 (40.4%)                   |         |    |
| Healthcare worker    | 22 (2.56%)   | 18 (2.93%)                   | 4 (1.63%)                    |         |    |
| Hospital acquired    | 11 (1.28%)   | 6 (0.98%)                    | 5 (2.04%)                    |         |    |
| Imported             | 95 (11.0%)   | 90 (14.6%)                   | 5 (2.04%)                    |         |    |
| Hypertension         | 324 (33.7%)  | 166 (25.2%)                  | 158 (52.3%)                  | <0.001  | 962 |
| DM                   | 335 (34.8%)  | 183 (27.7%)                  | 152 (50.3%)                  | <0.001  | 962 |
| CVD                  | 79 (8.21%)   | 33 (5.00%)                   | 46 (15.2%)                   | <0.001  | 962 |
| Chronic lung disease | 87 (9.04%)   | 52 (7.88%)                   | 35 (11.6%)                   | 0.082   | 962 |
| Chronic kidney disease | 43 (4.47%) | 21 (3.18%)                   | 22 (7.28%)                   | 0.007   | 962 |
| Immuno-compromised host | 16 (1.66%) | 10 (1.52%)                   | 6 (1.99%)                    | 0.795   | 962 |
| Pneumonia            | 527 (54.8%)  | 252 (38.2%)                  | 275 (91.1%)                  | <0.001  | 962 |
| ARDS                 | 140 (14.6%)  | 34 (5.15%)                   | 106 (35.1%)                  | <0.001  | 962 |
| ICU admission        | 149 (15.5%)  | 36 (5.45%)                   | 113 (37.4%)                  | <0.001  | 962 |
| ICU duration of stay (number of days [IQR]) | 13.0 [1.75; 63.8] | 13.0 [1.00; 66.1] | 13.0 [2.00; 58.0] | 0.474   | 151 |
| Admission to discharge (number of days [IQR]) | 15.0 [2.00; 52.0] | 14.0 [2.00; 39.5] | 18.0 [5.00; 60.0] | <0.001  | 950 |
| Mortality            | 87 (9.04%)   | 24 (3.64%)                   | 63 (20.9%)                   | <0.001  | 962 |

Data are presented as counts and percentages (n, %) unless otherwise specified. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; BMI = body mass index; DM = diabetes mellitus; CVD = cardiovascular disease; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range.

Table 2. Signs and Symptoms of SARS-CoV-2 Patients Stratified by Anticoagulation Therapy.

|                      | [ALL] N = 962 | Anticoagulation = no N = 660 | Anticoagulation = yes N = 302 | p-value | N |
|----------------------|--------------|------------------------------|-------------------------------|---------|---|
| Asymptomatic         | 155 (16.1%)  | 147 (22.3%)                  | 8 (2.65%)                     | <0.001  | 962 |
| Headache             | 100 (10.4%)  | 73 (11.1%)                   | 27 (8.94%)                    | 0.376   | 962 |
| Sore throat          | 93 (9.67%)   | 74 (11.2%)                   | 19 (6.29%)                    | 0.023   | 962 |
| Fever                | 547 (56.9%)  | 337 (51.1%)                  | 210 (69.5%)                   | <0.001  | 962 |
| Dry cough            | 459 (47.7%)  | 292 (44.2%)                  | 167 (55.3%)                   | 0.002   | 962 |
| Productive cough     | 68 (7.07%)   | 42 (6.36%)                   | 26 (8.61%)                    | 0.260   | 962 |
| SOB                  | 309 (32.1%)  | 135 (20.5%)                  | 174 (57.6%)                   | <0.001  | 962 |
| Fatigue or myalgia   | 216 (22.5%)  | 148 (22.4%)                  | 68 (22.5%)                    | >0.99   | 962 |
| Diarrhea             | 113 (11.7%)  | 76 (11.5%)                   | 37 (12.3%)                    | 0.825   | 962 |
| Nausea               | 60 (6.24%)   | 39 (5.91%)                   | 21 (6.95%)                    | 0.633   | 962 |
| Vomiting             | 59 (6.13%)   | 35 (5.30%)                   | 24 (7.95%)                    | 0.149   | 962 |
| Change of taste or smell | 34 (3.53%) | 27 (4.09%)                   | 7 (2.32%)                     | 0.232   | 962 |

Data are presented as counts and percentages (n, %) unless otherwise specified. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOB = shortness of breath.

Lactate dehydrogenase, C-reactive protein, procalcitonin, D-dimer, high-sensitivity serum troponin, ferritin, creatinine kinase, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, and direct bilirubin levels, compared to their counterparts. In contrast, patients not receiving anticoagulation therapy had increased levels of hemoglobin and albumin, and lymphocyte count, compared to their counterparts (Table 3).

Treatment Modalities in Hospital

Table 4 summarizes medication prescribed for the study patients, depending on their anticoagulation status. The rates
of current use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and statins were higher in the anticoagulation group than in the non-anticoagulation group. The use of antibiotics \( n = 246 \) \( (81.5\%) \), methylprednisolone \( n = 101 \) \( (33.4\%) \), dexamethasone \( n = 59 \) \( (19.5\%) \), azithromycin \( n = 14 \) \( (4.6\%) \), lopinavir-ritonavir \( n = 61 \) \( (20.2\%) \), tocilizumab \( n = 15 \) \( (5\%) \), and hydrocortisone \( n = 18 \) \( (6\%) \) was more common in the anticoagulation group than in the non-anticoagulation group. In contrast, the use of vitamin C effervescent tablets \( n = 434 \) \( (65.8\%) \) was more common in the non-anticoagulation group.

### Table 4. Medication Prescribed to Patients with SARS-CoV-2, Stratified by Anticoagulation Therapy.

|                       | [ALL] \( N = 962 \) | Anticoagulation = no \( N = 660 \) | Anticoagulation = yes \( N = 302 \) | p-value | N |
|-----------------------|---------------------|-----------------------------------|-----------------------------------|---------|---|
| Antibiotics           | 443 (46.0%)         | 197 (29.8%)                       | 246 (81.5%)                       | <0.001  | 962 |
| Methylprednisolone    | 146 (15.2%)         | 45 (6.82%)                        | 101 (33.4%)                       | <0.001  | 962 |
| Dexamethasone         | 75 \( (7.80\%) \)   | 16 \( (2.42\%) \)                | 59 \( (19.5\%) \)                | <0.001  | 962 |
| Vitamin C effervescent tablets | 606 \( (63.0\%) \) | 434 \( (65.8\%) \)               | 172 \( (57.0\%) \)               | 0.011   | 962 |
| Azithromycin          | 18 \( (1.87\%) \)   | 4 \( (0.61\%) \)                 | 14 \( (4.64\%) \)                | <0.001  | 962 |
| Vitamin D             | 334 \( (34.7\%) \)  | 231 \( (35.0\%) \)               | 103 \( (34.1\%) \)               | 0.844   | 962 |
| Hydroxychloroquine    | 113 \( (11.7\%) \)  | 64 \( (9.70\%) \)                | 49 \( (16.2\%) \)                | 0.005   | 962 |
| KALETRA (lopinavir/ritonavir) | 110 \( (11.4\%) \) | 49 \( (7.42\%) \)                | 61 \( (20.2\%) \)                | <0.001  | 962 |
| ACTEMRA (tocilizumab) | 17 \( (1.77\%) \)   | 2 \( (0.30\%) \)                 | 15 \( (4.97\%) \)                | <0.001  | 962 |
| Hydrocortisone        | 22 \( (2.29\%) \)   | 4 \( (0.61\%) \)                 | 18 \( (5.96\%) \)                | <0.001  | 962 |
| Current use of ACE inhibitor | 87 \( (10.5\%) \) | 50 \( (8.38\%) \)                | 37 \( (16.2\%) \)                | 0.002   | 826 |
| Current use of ARB    | 110 \( (13.3\%) \)  | 57 \( (9.56\%) \)                | 53 \( (23.0\%) \)                | <0.001  | 826 |
| Current use of statin | 219 \( (25.6\%) \)  | 114 \( (18.8\%) \)               | 105 \( (42.0\%) \)               | <0.001  | 855 |
| **OXYGEN requirements:** |                     |                                   |                                   | <0.001  | 887 |
| High oxygen requirement | 139 \( (15.7\%) \) | 35 \( (5.86\%) \)               | 104 \( (35.9\%) \)               |         |     |
| Low oxygen requirements | 249 \( (28.1\%) \) | 102 \( (17.1\%) \)               | 147 \( (50.7\%) \)               |         |     |
| None                  | 499 \( (56.3\%) \)  | 460 \( (77.1\%) \)               | 39 \( (13.4\%) \)                |         |     |

The data are presented as counts and percentages (n, %), unless stated otherwise.

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers.
common in the non-anticoagulation group than in the coagulation group. Patients receiving anticoagulation treatment had either high (n = 104 [35.9%]) or low oxygen (n = 147 [50.7%]) requirements; in contrast, patients not receiving anticoagulation treatment had no oxygen requirements (n = 460 [77.1%]).

**Multivariable Logistic Regression Model**

Therapeutic anticoagulation agent use (odds ratio [OR] = 2.21, 95% confidence interval [CI], 1.28-3.92, p = 0.005), age (OR = 1.04, 95% CI, 1.02-1.06, p < 0.001), hypertension (OR = 2.30, 95% CI, 1.29-4.17, p = 0.005), COVID-19 pneumonia (OR = 4.86, 95% CI, 1.96-14.75, p = 0.002), and methylprednisolone use (OR = 2.12, 95% CI, 1.25-3.58, p = 0.005) were associated with all-cause cumulative mortality risk (Table 5).

**Mortality Risk**

The Cox proportional hazards model revealed that anticoagulation treatment was a significant predictor of mortality (LL = 27.46, df=1, p<0.001). At any time, the risk of death among patients not receiving anticoagulation treatment was 70% lower than that among patients receiving this treatment (Table 6). The Kaplan-Meier survival curves yielded consistent findings (Figure 2).

### Table 6. Cox Proportional Hazards Regression Coefficients for Anticoagulation.

| Variable                  | B    | SE  | 95% CI        | z    | p   | HR   |
|---------------------------|------|-----|---------------|------|-----|------|
| Anticoagulation = no      | -1.20| 0.24| [-1.67, -0.72]| -4.93| < .001| 0.30 |

Multivariable analyses were conducted using logistic regression models utilizing the simultaneous method. The models were adjusted for the characteristics listed in the first column. aOR, adjusted odds ratio; CI, confidence interval; aP-value, adjusted p-value; DM = diabetes mellitus.

### Figure 2. Kaplan-Meier method-estimated mortality rates, stratified by anticoagulation status, depending on time since admission.
Discussion

This study revealed mean age of the patients receiving therapeutic anticoagulation agents was 57.2 ± 14.6 years. ICU admissions were relatively common in this group. Approximately 36% of the patients receiving therapeutic anticoagulation agents had high oxygen requirements. Overall, 91% of patients in the therapeutic anticoagulation group had pneumonia. Age, hypertension, pneumonia, therapeutic anticoagulation, and methylprednisolone use were found to be strong predictors of in-hospital mortality. In elderly hypertensive COVID-19 patients on therapeutic anticoagulation were found to have 2.3 times higher risk of in-hospital mortality. All cause in-hospital mortality rate in the therapeutic anticoagulation group was up to 21%. Further prospective studies are required to elucidate the impact of anticoagulation therapy on in-hospital mortality rates among SARS-CoV-2 patients that meet certain clinical criteria.

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Statement of Ethics

The study protocol was approved by the standing committee for the coordination of health and medical research at the Ministry of Health in Kuwait (institutional review board number 2020/1422).

Author Contributions

MAR designed the study. MAR and RR participated in data analysis and wrote the manuscript. AAS and JP performed the statistical analysis and reviewed the manuscript. The remaining authors collected the data. All authors had access to the data and took responsibility for the integrity and accuracy of data analysis. All authors have read and approved the manuscript.

Data Availability Statement

The data that support the results of the study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

Declaration of Conflicting Interests

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References

1. Tacquard C, Mansour A, Godon A, et al. Impact of high-dose prophylactic anticoagulation in critically ill patients with COVID-19 pneumonia. Chest. 2021;159(6):2417-2427.
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. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1421-1424.
4. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089-1098.
5. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145-147.

6. Middeldorp S, Coppens M, Haaps T, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost.* 2020;18:1995-2002.

7. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalized patients with COVID-19 in a New York city health system. *JAMA.* 2020;324(8):799-801.

8. Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. *J Am Coll Cardiol.* 2020;76:1815-1826.

9. Al-Samkari HGS, Karp Leaf R, Wang W, et al. Thrombosis, anticoagulation with in-hospital survival among hospitalized patients with COVID-19 in the United States. *Res Pract Thromb Haemost.* 2021;164(5):622-632.

10. Ferguson J, Volk S, Vondracek T, Flanigan J, Chernaik A. Empiric therapeutic anticoagulation and mortality in critically ill patients with respiratory failure from SARS-CoV-2: a retrospective cohort study. *J Clin Pharmacol.* 2020;60:1411-1415.

11. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *J Am Coll Cardiol.* 2020;76:122-124.

12. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(4):844-847.

13. Pesavento R, Ceccato D, Pasquetto G, et al. The hazard of (sub)therapeutic doses of anticoagulants in non-critically ill patients with COVID-19: the Padua province experience. *J Thromb Haemost.* 2020;18:2629-2635.

14. Ho GD, Dusendang JR, Schmittiel J, Kavecansky J, Tavakoli J, Pai A. Antiplatelet and antithrombotic use not associated with improvement in severe outcomes in COVID-19 patients. *Blood.* 2020;136:59.

15. Al-Jarallah M, Rajan R, Saber AAL, et al. In-hospital mortality in SARS-CoV-2 stratified by hemoglobin levels: a retrospective study. *elHaem.* 2021. doi: 10.1002/jha2.195.

16. Al-Jarallah M, Rajan R, Dashiti R, et al. In-hospital mortality in SARS-CoV-2 stratified by serum 25-hydroxy-vitamin D levels: a retrospective study. *J Med Virol.* 2021;93:5880-5885.

17. Alroomi M, Rajan R, Omar AA, et al. Ferritin level: a predictor of severity and mortality in hospitalized COVID-19 patients. *Immun Inflamm Dis.* 2021;9(4):1648-1655.

18. Al-Jarallah M, Rajan R, Dashiti R, et al. In-hospital mortality in SARS-CoV-2 stratified by sex differences: a retrospective cross-sectional cohort study. *Ann Med Surg (Lond).* 2022;79:104026. doi: 10.1016/j.amsu.2022.104026. PMID: 35757308; PMCID: PMC9212930.

19. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and functional limitation: data from the third national health and nutrition examination. *J Intern Med.* 2003;254(6):540-547. doi:10.1111/j.1365-2796.2003.01211.x.

20. Belsky JA, Tullius BP, Lamb MG, Sayegh R, Stanek JR, Auletta JJ. COVID-19 in immunocompromised patients: a systematic review of cancer, hematopoietic cell and solid organ transplant patients. *J Infect.* 2021;82(3):329-338. doi:10.1016/j.jinf.2021.01.022.

21. Lee EE, Hwang W, Song KH, et al. Predication of oxygen requirement in COVID-19 patients using dynamic change of inflammatory markers: CRP, hypertension, age, neutrophil and lymphocyte (CHANeL). *Sci Rep.* 2021;11:13026. https://doi.org/10.1038/s41598-021-92418-2.

22. Laine T, Reyes EM. Tutorial: survival estimation for Cox regression models with time-varying coefficients using SAS and R. *J Stat Softw.* 2014;61:1-23.

23. Pawlowski C, Venkatakrishnan AJ, Kirkup C, et al. Enoxaparin is associated with lower rates of mortality than unfractionated Heparin in hospitalized COVID-19 patients. *EClinicalMedicine.* 2021;33:100774. doi:10.1016/j.eclinm.2021.100774.

24. Billett HH, Reyes-Gil M, Szymanski J, et al. Anticoagulation in COVID-19: effect of enoxaparin, heparin, and apixaban on mortality. *Thromb Haemost.* 2020;120(12):1691-1699.

25. ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators, et al. Therapeutic anticoagulation with heparin in non-critically ill patients with COVID-19. *N Engl J Med.* 2021;385(9):790-802.

26. Nakazawa D, Ishizu A. Immunothrombosis in severe COVID-19. *EBioMedicine.* 2020;59:102942. 2.

27. Manne BK, Denorme F, Middleton EA, et al. Platelet gene expression and function in patients with COVID-19. *Blood.* 2020;136:1317-1329.

28. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, crosssectional study. *Lancet Haematol.* 2020;7(8):e575-e582.

29. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. *Blood.* 2020;136(11):1330-1341.

30. Chow JH, Khanna AK, Kethireddy S, et al. Aspirin use is associated with decreased mechanical ventilation, intensive care unit admission, and in-hospital mortality in hospitalized patients with coronavirus disease 2019. *Anesth Analg.* 2021;132(4):930-941.

31. Fröhlich GM, Jeschke E, Eichler U, et al. Impact of oral anticoagulation on clinical outcomes of COVID-19: a nationwide cohort study of hospitalized patients in Germany. *Clin Res Cardiol.* 2021;110:1041-1050.

32. Ionescu F, Jaiyesimi I, Petrescu I, et al. Association of anticoagulation dose and survival in hospitalized COVID-19 patients: a retrospective propensity score-weighted analysis. *Eur J Haematol.* 2021;106:165-174.

33. Sadeghipour P, Talasaz AH, Rashidi F, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *JAMA.* 2021;325:1620-1630.

34. White D, MacDonald S, Bull T, et al. Heparin resistance in COVID-19 patients in the intensive care unit. *J Thromb Thrombolysis.* 2020;50:287-291.

35. Xue M, Zeng Y, Qu H-Q, et al. Heparin- binding protein levels correlate with aggravation and multiorgan damage in severe COVID-19. *ERJ Open Res.* 2021;7(1):00741-002020.
36. Hsu A, Liu Y, Zayac AS, Olszewski AJ, Reagan JL. Intensity of anticoagulation and survival in patients hospitalized with COVID-19 pneumonia. *Thromb Res*. 2020;196:375-378.

37. Lu YF, Pan LY, Zhang WW, et al. A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19. *Int J Infect Dis*. 2020;100:34-41.

38. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *J Thromb Thrombolysis*. 2021;51(4):1107-1110.

39. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099.

40. Hozayen SM, Zychowski D, Benson S, et al. Outpatient and inpatient anticoagulation therapy and the risk for hospital admission and death among COVID-19 patients. *EClinicalMedicine*. 2021;41:101139. doi:10.1016/j.eclinm.2021.101139.

41. Al Saleh M, Alotaibi N, Schrapp K, et al. Risk factors for mortality in patients with COVID-19: the Kuwait experience. *Med Princ Pract*. 2021. doi: 10.1159/000522166