

# In-hospital Mortality Rates in SARS-CoV-2 Patients Treated with Enoxaparin and Heparin

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## Abstract

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/m<sup>2</sup>) 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.<sup>1</sup> 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).<sup>2-5</sup> In these patients, the risk of venous thromboembolism has been estimated at 47%.<sup>6</sup> Thrombosis has been reported as an independent predictor of mortality in SARS-CoV-2 patients.<sup>7</sup> Some studies have suggested that the use of therapeutic anticoagulation agents may reduce the risk of mortality; however, the evidence remains inconclusive.<sup>8-13</sup> In fact, a study has reported no improvement in outcome with the use of anticoagulation or anti-platelet agents in SARS-CoV-2 patients.<sup>14</sup>

## 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  $\geq 18$  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.<sup>15-17</sup> 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.<sup>18</sup> 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.<sup>19</sup> Patients receiving immunosuppressive therapy were defined as immunocompromised

patients.<sup>20</sup> 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, except 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.<sup>21</sup> 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.

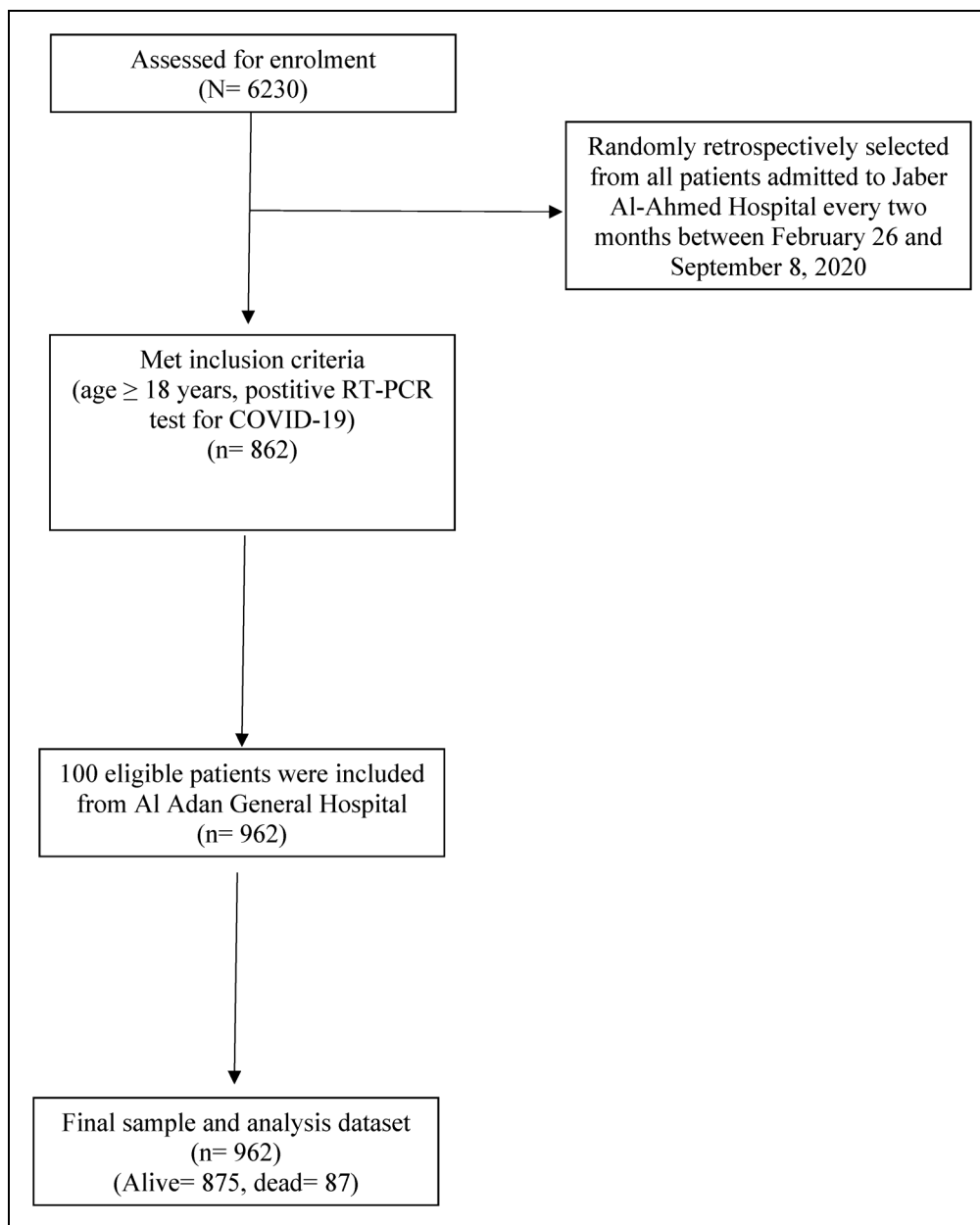
### Statistical Analysis

Frequencies, percentages, means  $\pm$  standard deviations (SD) and medians  $\pm$  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).<sup>22</sup>

## Results

### Baseline Characteristics

The patients' baseline characteristics are presented in Table 1. In the group receiving anticoagulation treatment ( $n = 302$ ; mean age,  $57.2 \pm 14.6$  years; mean BMI,  $29.8 \pm 6.53$  kg/m<sup>2</sup>), 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,  $47.0 \pm 15.4$  years; mean BMI



**Figure 1.** Study flowchart.

$28.6 \pm 5.97 \text{ kg/m}^2$ ), 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/m <sup>2</sup>	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
<b>Smoking:</b>				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%)		
<b>Source of transmission:</b>				<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%)		
<b>Hypertension</b>	324 (33.7%)	166 (25.2%)	158 (52.3%)	<0.001	962
<b>DM</b>	335 (34.8%)	183 (27.7%)	152 (50.3%)	<0.001	962
<b>CVD</b>	79 (8.21%)	33 (5.00%)	46 (15.2%)	<0.001	962
<b>Chronic lung disease</b>	87 (9.04%)	52 (7.88%)	35 (11.6%)	0.082	962
<b>Chronic kidney disease</b>	43 (4.47%)	21 (3.18%)	22 (7.28%)	0.007	962
<b>Immunocompromised host</b>	16 (1.66%)	10 (1.52%)	6 (1.99%)	0.795	962
<b>Pneumonia</b>	527 (54.8%)	252 (38.2%)	275 (91.1%)	<0.001	962
<b>ARDS</b>	140 (14.6%)	34 (5.15%)	106 (35.1%)	<0.001	962
<b>ICU admission</b>	149 (15.5%)	36 (5.45%)	113 (37.4%)	<0.001	962
<b>ICU duration of stay (number of days [IQR])</b>	13.0 [1.75; 63.8]	13.0 [1.00; 66.1]	13.0 [2.00; 58.0]	0.474	151
<b>Admission to discharge (number of days [IQR])</b>	15.0 [2.00; 52.0]	14.0 [2.00; 39.5]	18.0 [5.00; 60.0]	<0.001	950
<b>Mortality</b>	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

**Table 3.** Baseline Laboratory Parameters of SARS-CoV-2 Patients, Stratified by Anticoagulation Therapy.

	[ALL] N = 951	Anticoagulation = no N = 650	Anticoagulation = yes N = 301	p-value	N
Hemoglobin (g/L)	127 [125;129]	131 [129;133]	114 [108;119]	<0.001	951
Platelets ( $10^9/L$ )	254 [244;265]	252 [242;262]	259 [237;277]	0.362	950
WBC ( $10^9/L$ )	6.70 [6.50;7.00]	6.30 [6.10;6.50]	8.30 [7.50;9.20]	<0.001	949
Neutrophils count	4.14 [4.00;4.40]	3.70 [3.40;3.83]	6.70 [6.00;7.60]	<0.001	948
Lymphocytes count	1.40 [1.40;1.50]	1.62 [1.60;1.70]	1.00 [0.90;1.10]	<0.001	948
Creatinine (umol/L)	76.0 [75.0;78.0]	74.0 [72.0;76.0]	85.0 [80.0;90.0]	<0.001	945
LDH (IU/L)	305 [290;322]	244 [232;262]	371 [360;398]	<0.001	641
CRP (mg/L)	49.0 [38.0;56.8]	21.0 [17.0;26.0]	102 [91.6;121]	<0.001	907
Procalcitonin (ng/mL)	0.09 [0.08;0.10]	0.07 [0.06;0.07]	0.34 [0.21;0.43]	<0.001	609
D-dimer (ng/mL)	360 [320;402]	256 [247;284]	608 [523;707]	<0.001	617
25 (OH) vitamin D (nmol/L)	41.0 [37.0;44.0]	41.0 [38.0;45.0]	34.0 [29.0;45.0]	0.384	239
Troponin I HS (ng/L)	9.00 [7.00;11.0]	6.00 [5.00;7.00]	16.0 [12.0;21.0]	<0.001	331
Ferritin (ng/mL)	449 [398;496]	316 [289;353]	696 [605;773]	<0.001	595
Creatinine kinase (IU/L)	88.0 [60.0;160]	64.0 [55.0;101]	311 [72.0;3147]	0.004	33
ALT (IU/L)	33.0 [31.0;35.0]	31.5 [29.0;34.0]	36.0 [32.0;41.0]	<0.001	942
AST (IU/L)	33.0 [32.0;35.0]	29.0 [28.0;31.0]	45.0 [41.0;47.0]	<0.001	941
ALP (IU/L)	69.0 [67.0;72.0]	67.0 [65.0;69.0]	78.0 [72.0;86.0]	<0.001	939
GGT (IU/L)	36.5 [33.0;41.0]	30.0 [27.0;33.0]	62.0 [51.0;76.0]	<0.001	802
Albumin (g/L)	35.3 [35.0;35.9]	36.8 [36.1;37.2]	31.0 [30.0;32.0]	<0.001	940
T. bilirubin (umol/L)	11.5 [11.0;11.8]	11.1 [10.6;11.6]	12.1 [11.4;13.0]	0.002	940
D. bilirubin (umol/L)	2.60 [2.40;2.70]	2.20 [2.10;2.30]	3.50 [3.20;4.00]	<0.001	926

Values are presented as median  $\pm$  interquartile range.

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WBC, white blood cells; LDH, lactate dehydrogenase; CRP, C-reactive protein; HS, high-sensitivity; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; T. bilirubin, total bilirubin; D. bilirubin, direct bilirubin

**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
<b>OXYGEN requirements:</b>				<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.

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

**Table 5.** Multivariable Logistic Regression Analysis of Overall in-Hospital Mortality Rates.

		Surviving	Dead	Univariable OR (95% CI, P-value)	Multivariable logistic regression aOR (95% CI, aP-value)
Therapeutic anticoagulation	yes	239 (79.1)	63 (20.9)	6.99 (4.32-11.64, $p < 0.001$ )	2.21 (1.28-3.92, $p = 0.005$ )
Age	Mean (SD)	48.9 (15.4)	63.5 (14.8)	1.06 (1.05-1.08, $p < 0.001$ )	1.04 (1.02-1.06, $p < 0.001$ )
Hypertension	yes	263 (81.2)	61 (18.8)	5.46 (3.41-8.97, $p < 0.001$ )	2.30 (1.29-4.17, $p = 0.005$ )
DM	yes	288 (86.0)	47 (14.0)	2.39 (1.54-3.75, $p < 0.001$ )	0.78 (0.45-1.34, $p = 0.371$ )
Pneumonia	yes	445 (84.4)	82 (15.6)	15.85 (7.04-45.38, $p < 0.001$ )	4.86 (1.96-14.75, $p = 0.002$ )
Fever	yes	485 (88.7)	62 (11.3)	1.99 (1.25-3.29, $p = 0.005$ )	1.50 (0.87-2.64, $p = 0.150$ )
Methylprednisolone	yes	107 (73.3)	39 (26.7)	5.83 (3.64-9.31, $p < 0.001$ )	2.12 (1.25-3.58, $p = 0.005$ )

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

**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

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%]).

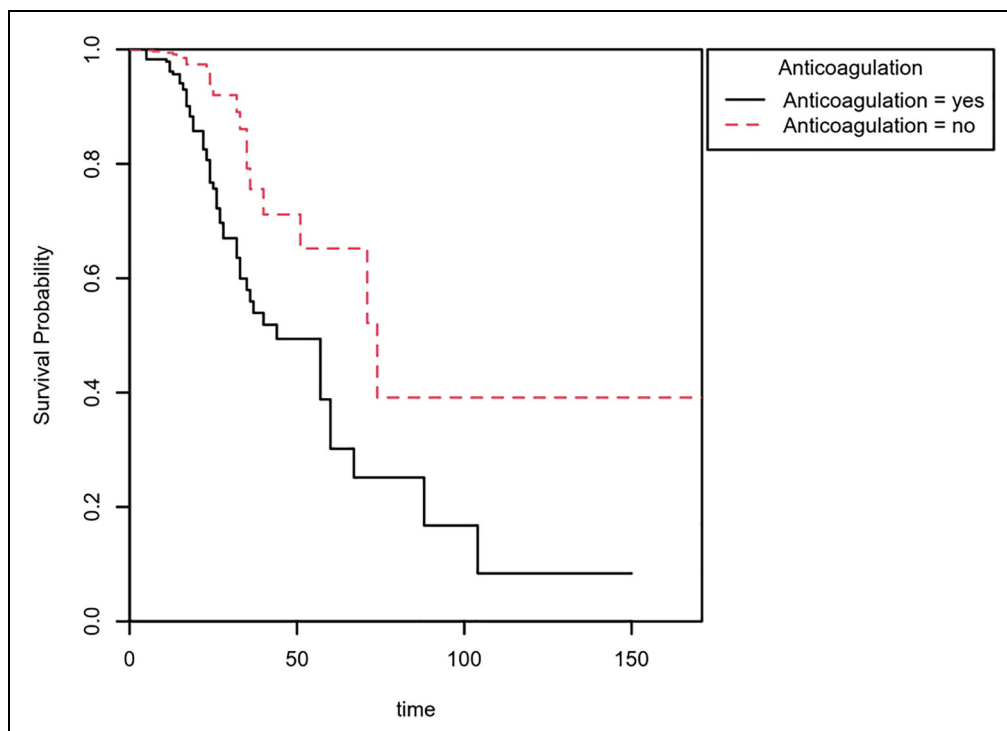
### Multivariable Logistic Regression Model

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).

**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  $57.2 \pm 14.6$  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%.

A study by Pawlowski *et al* found that unfractionated heparin use was associated with higher risk of 28-day mortality.<sup>23</sup> Billett *et al* showed that apixaban and enoxaparin have comparable mortality risk reducing effects in patients with SARS-CoV-2 infection.<sup>24</sup> Meanwhile, the ACTIV-4a trial revealed no survival benefits of therapeutic compared to prophylactic anticoagulation treatment in critically ill SARS-CoV-2 patients.<sup>25</sup> The evidence on the prophylactic use of anti-platelets in SARS-CoV-2 patients remains inconclusive.<sup>26–30</sup>

The use of anticoagulation agents has been associated with survival benefits in SARS-CoV-2 patients.<sup>31,32</sup> However, intravenous heparin did not improve outcomes in critically ill SARS-CoV-2 patients,<sup>33</sup> and therapeutic anticoagulation was found non-beneficial in many studies.<sup>34,35</sup> Hsu *et al* reported mortality risk reducing effects of high-intensity anticoagulation treatment in SARS-CoV-2 patients.<sup>36</sup> A meta-analysis by Lu *et al* revealed that the use of antithrombotic medications in SARS-CoV-2 patients did not reduce mortality risks.<sup>37</sup> Overall, most studies examining the impact of anticoagulation agent use on mortality risks reported negative findings.<sup>38, 39</sup> Patients who had outpatient anticoagulation for a period of 90 days were found to have reduced rate of hospitalization.<sup>40</sup>

## Limitations

Patients who received anticoagulation therapy in this study had higher prevalence rates of hypertension, DM, cardiovascular disease, and chronic kidney disease; some of these baseline clinical characteristics were independent predictors of COVID-19-related mortality in the population of Kuwait.<sup>41</sup> This study included all SARS-CoV-2-positive patients regardless of disease severity.

## Conclusions

In this study 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

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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