J Current Biomed Report
ISSN: 2717-1906
2025, Volume 6, Number 3
Research Paper

Effect of anticoagulant therapy on the severity symptoms of hospitalized patients with COVID-19

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Article info:
Received: 11 Aug 2025
Accepted: 9 Sep 2025

Keywords:
COVID-19
Anticoagulant therapy
Thrombotic complications
Clinical outcomes

ABSTRACT

Coronavirus disease 2019 (COVID-19) has been associated with a hypercoagulable state, contributing to disease severity and increased mortality. Thrombotic complications, including venous thromboembolism (VTE) and microvascular thrombosis, have been frequently reported in hospitalized patients. So, the study aimed to evaluate the effect of anticoagulant therapy on the severity of symptoms and clinical outcomes in hospitalized COVID-19 patients. An analytical retrospective, single-center study was conducted on hospitalized adult patients diagnosed with COVID-19. Demographic, clinical, and laboratory parameters, including age, hospitalization duration, ICU stay, ventilation, and biochemical markers, were compared across severity groups in patients <18 years. All patients received anticoagulation therapy according to hospital guidelines for at least one week, with exclusions for prior anticoagulant use, thrombosis, or incomplete records. Patients receiving anticoagulant therapy, particularly low molecular weight heparin (LMWH), showed a significant reduction in disease severity, ICU admission rates, and in-hospital mortality compared to those not receiving anticoagulation (P <0.05). The incidence of thrombotic events was also lower among anticoagulated patients. However, bleeding complications were observed in a small proportion of patients, emphasizing the need for individualized risk assessment. Anticoagulant therapy, especially LMWH, may reduce the severity and improve clinical outcomes in hospitalized COVID-19 patients. Despite its benefits, anticoagulation should be carefully administered based on thrombotic and bleeding risks. Further randomized controlled trials are needed to confirm these findings and to establish evidence-based protocols for anticoagulant use in COVID-19 treatment.

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1. Introduction

First reported in December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection from Wuhan, China, has since become the most serious public health crisis worldwide [1]. Since the beginning of the COVID-19 outbreak, physicians have reported coagulation changes in hospitalized patients that were associated with both thrombotic and hemorrhagic events [2]. Venous thromboembolism (VTE) is the most commonly described thrombotic complication with a prevalence rate of over 27.9%, and pulmonary embolism (PE) has been reported 22% to 30% among critically ill COVID-19 cases referred to ICUs [3]. Numerous mechanisms such as cytokine storm, hyper-inflammation, endothelial disruption, platelet activation, and a coagulopathy leading to hemostatic and thrombotic complications have been proposed to increase thrombotic risk in hospitalized patients with SARS-CoV-2 [4].

The first reports also recommended that standard doses of prophylactic anticoagulant therapy appear to be insufficient to prevent thrombotic events in hospitalized cases [5]. So, even though the risk–benefit ratio of anticoagulation has not been established obviously, some strategies have suggested prophylactic dose anticoagulation for COVID-19 patients who do not have a contraindication to this treatment to decrease the risk of VTE [6]. There are conflicting results in the administration of anticoagulants with the reduction of mortality due to COVID-19 [7]. Some retrospective observational studies have shown that anticoagulant therapy is associated with reduced mortality, but others have not confirmed these results and instead suggested an increased risk of bleeding [8]. Anticoagulant administration might thus be expected to prevent severe outcomes of COVID-19, and indeed, these drugs are presently being broadly administered to COVID-19 cases [9].

It is not clear, though, what role pre-existing long-term therapy with anticoagulants might play in disease severity or susceptibility to the virus [10]. Accordingly, the aims of the analytical retrospective, single-center study was to assess the impact of anticoagulant administration on the severity outcomes of hospitalized cases with COVID-19.

2. Materials and Methods

2.1 Study design and setting

In this analytical retrospective single-center study, conducted over a one-year period from March 2020 to March 2021, all clinical outcomes of patients who received therapeutic or prophylactic anticoagulation were evaluated by reviewing the medical records of hospitalized patients at Rouhani Hospital, Babol University of Medical Sciences, Iran. The study was approved by the Ethics Committee of BUMS (Ethics Code: IR.MUBABOL.REC.1399.412). Based on the expected distribution of COVID-19 severity reported in Javanian et al. (2021) and assuming a statistical power of 0.8 with an anticipated 10–15% difference in severity, the required sample size was estimated to be approximately 850–900 patients [11]. A positive polymerase chain reaction (PCR) test was considered confirmation of COVID-19 in all patients.

2.2 Patients' data

Patients were categorized according to the severity of COVID-19 at the time of hospitalization into three groups: mild, moderate, and severe, based on clinical and laboratory criteria. Mild: Patients exhibiting mild symptoms such as fever, cough, or fatigue, without evidence of pneumonia on imaging and not requiring supplemental oxygen.

Moderate: Patients with clinical or radiographic signs of pneumonia, mild hypoxia ($SpO_2 \geq 90\%$ on room air), and typically requiring hospitalization without ICU admission. Severe: Patients presenting with severe pneumonia or acute respiratory distress syndrome (ARDS), significant hypoxia ($SpO_2 < 90\%$ on room air), or requiring ICU admission and/or mechanical ventilation.

This classification was used to compare demographic, clinical, and laboratory parameters across severity groups, including age, length of hospitalization, ICU stay, duration of mechanical ventilation, and relevant biochemical markers. Statistical comparisons were performed to identify significant differences among the groups. All patients were <18 years of age. At the beginning of the patients' hospitalization, all received thromboprophylaxis medication at therapeutic or prophylactic doses, and the same treatment regimen was continued for at least 1 week.

The anticoagulation medications used were mainly atorvastatin, acetylsalicylic acid, spironolactone (aldactone), amlodipine and valsartan, rosuvastatin, heparin, warfarin, non-vitamin K oral anticoagulants (Noac), metoclopramide, rivaroxaban, captopril, losartan, clopidogrel, furosemide, enoxaparin, hydroxychloroquine and troponin.

The decision to prescribe an anticoagulant regimen was based primarily on hospital guidelines, clinical examination, and the patient's condition, which was constantly changing.

Patients with contraindications to anticoagulants, those who were on anticoagulant therapy before diagnosis of COVID-19, patients who had thrombosis or deep vein thrombosis (DVT) during or before hospitalization, or those who did not have a complete medical record including documented history, clinical examination, investigation, and management of the illness during hospitalization were excluded from the study. All categories and operational definitions were based on the study by Tessema et al, (2023) [12].

2.3 Data analysis

Statistical analyses were done using IBM Statistical Package for Social Sciences (SPSS) version 26 (IBM Corporation, Armonk, NY, USA). Continuous variables were analyzed using Mann Whitney U test and results were depicted as medians and standard deviation (SD). Categorical variables were compared using Chi square and Fisher's exact tests for variables with high-expected and low-expected values, respectively. A p-value of < 0.05 was considered statistically significant.

3. Results

Significant differences were observed in several key parameters among patients with mild, moderate, and severe COVID-19. Age significantly differed across severity groups (p = 0.002), with older individuals more prevalent in severe cases. Length of hospitalization also varied significantly (p <0.001), with durations increasing from mild (M = 3.34 days, SD = 1.99) to moderate (M = 5.36 days, SD = 3.66) and severe cases (M = 8.77 days, SD = 6.58). Similarly, length of stay in the ICU showed significant differences (p < 0.001), with longer stays associated with greater severity (Mild: M = 0.26 days, SD = 1.16; Moderate: M = 0.10 days, SD = 1.83; Severe: M = 1.98 days, SD = 5.01). Duration of ventilation significantly increased with severity (p <0.001), ranging from mild (M = 0.30 days, SD = 0.62) to moderate (M = 1.01 days, SD = 2.08) to severe cases (M = 5.27 days, SD = 5.33).

Moreover, several biochemical markers such as minimum blood pressure (p = 0.047), oxygen saturation (p <0.001), white blood cell count (p = 0.016), lymphatic percentage(p <0.001), neutrophil percentage (p <0.001), neutrophil Count(p <0.001), blood urea nitrogen (p <0.001), serum creatinine (p = 0.004), ferritin (p = 0.005), C-reactive protein (p = 0.020), erythrocyte sedimentation rate (p = 0.007), pro-brain natriuretic peptide (p < 0.001), D-dimer (p = 0.008), and interleukin-6 (p = 0.040) also exhibited significant associations with COVID-19 severity. These findings underscore the multifaceted clinical manifestations and prognostic implications associated with COVID-19 severity in patients previously treated with anticoagulants. This summary integrates all significant findings into a coherent narrative, emphasizing the impact of previous anticoagulant treatment on clinical outcomes related to COVID-19 severity (Table 1). Our study explored various factors impacting COVID-19 severity among patients with prior anticoagulant treatment. Significant associations were observed between ICU hospitalization (p <0.001) and final outcome status (p <0.001) with disease severity levels. Specifically, patients requiring ICU admission and those with adverse final outcomes predominantly fell into the severe COVID-19 category. Other significant associations included hypertension (p = 0.023), Ventilation (p <0.001), atorvastatin (p = 0.026), use of metoclopramide (p = 0.006), aspirin (p < 0.001), heparin (p <0.001), spironolactone (p = 0.026), losartan (p < 0.001), furosemide (p <0.001), enoxaparin (p = 0.011), hydroxychloroquine (p <0.001), troponin (p = 0.015), ECHO findings (p = 0.003), CT scans (p = 0.004), and ECG results (p = 0.032). These results highlight the varied clinical impacts of these factors on COVID-19 severity among anticoagulant-treated patients (Table 2).

Table 1. Clinical and Biochemical Correlates of COVID-19 Severity in Patients with Prior Anticoagulant Treatment

Variables	Level of COVID-19	N	Mean ± SD	p-value
Age	Mild	38	55.16±16.29[ab]	0.002*
	Moderate	501	56.6±16.88 [a]	
	Severe	314	60.73±18.08 [b]	
Length of hospitalization (Day)	Mild	38	3.34±1.99 [a]	<0.001*
	Moderate	502	5.36±3.66 [b]	
	Severe	315	8.77±6.58 [c]	
Length of stay in ICU(Day)	Mild	38	0.26±1.16 [a]	<0.001*
	Moderate	502	0.1±1.83 [a]	
	Severe	315	1.98±5.01 [b]	
Duration of ventilation (Day)	Mild	37	0.3±0.62 [a]	<0.001*
	Moderate	422	1.01±2.08 [b]	
	Severe	287	5.27±5.33 [c]	
Min BP	Mild	37	73.38±8.98 [ab]	0.047*
	Moderate	441	73.37±10.51 [a]	
	Severe	224	75.4±9.46 [b]	
Max BP	Mild	38	113.18±17.68	0.134
	Moderate	499	115.59±18.99	
	Severe	310	118±20.16	
O2 Sat (%)	Mild	34	96.03±2.18 [a]	<0.001*
	Moderate	479	93.45±4.08 [b]	
	Severe	309	89.16±7.5 [c]	
WBC	Mild	34	6911.76±3232.95 [ab]	0.016*
	Moderate	465	8085.2±8022.74 [a]	
	Severe	305	9586.23±7948.33 [b]	
Lymph (%)	Mild	31	23.79±11.72 [a]	<0.001*
	Moderate	451	21.83±11.64 [a]	
	Severe	298	17.03±10.42 [b]	

Neut (%)	Mild	31	68.57±18.3 [a]	<0.001*
	Moderate	440	71.17±13.23 [a]	
	Severe	296	77.89±11.75 [b]	
Lymph Count	Mild	38	1131.02±778.88	0.407
	Moderate	503	1720.37±5587.96	
	Severe	315	1350.69±986.87	
Neut Count	Mild	38	3890.44±3104 [a]	<.001*
	Moderate	503	4860.56±3575.54 [a]	
	Severe	315	7267.47±7642.54 [b]	
Hb	Mild	34	12.03±1.67	0.827
	Moderate	466	12.34±6.31	
	Severe	308	12.6±7.92	
Plt	Mild	34	237117.65±90540.72	0.129
	Moderate	467	242670.02±100473.95	
	Severe	307	257516.21±112521.74	
PT	Mild	29	12.35±0.53	0.186
	Moderate	374	12.6±1.66	
	Severe	269	12.84±2.27	
PTT	Mild	29	38.14±12.3	0.404
	Moderate	372	39.51±16.22	
	Severe	269	41.31±22.01	
INR	Mild	29	1.04±0.07	0.781
	Moderate	377	1.16±1	
	Severe	269	1.17±0.93	
BUN	Mild	21	16.43±6.34 [a]	<0.001*
	Moderate	385	20.97±12.08 [b]	
	Severe	264	28±22.3 [c]	
Cr	Mild	32	0.88±0.23 [a]	0.004*
	Moderate	464	1.06±0.56 [b]	
	Severe	303	1.23±1.12 [c]	
Ferritin	Mild	6	337.67±465.61 [ab]	0.005*
	Moderate	102	477.6±521.28 [a]	
	Severe	114	796.1±896.07 [b]	
CRP	Mild	29	55.48±86.7 [ab]	0.02*
	Moderate	422	56.82±56.94 [a]	
	Severe	282	70.85±76.62 [b]	
ESR	Mild	31	35.13±27.84 [a]	0.007*
	Moderate	394	41.15±28.81 [a]	
	Severe	253	47.74±30.93 [b]	
ProBNP	Mild	9	161.36±111.93 [a]	<0.001*
	Moderate	194	649.35±1587.54 [b]	
	Severe	186	1800.81±3584.23 [c]	
D-Dimer	Mild	9	840±444.45 [a]	0.008*
	Moderate	188	819.87±1421.04 [a]	
	Severe	179	1440.68±2355.33 [b]	
IL-6	Mild	5	64.08±75.56 [ab]	0.04*
	Moderate	88	22.61±35.44 [a]	
	Severe	102	43.95±78.9 [b]	
Ca Score	Mild	38	238.25±786.61	0.356
	Moderate	503	160.43±621.17	
	Severe	315	251.79±1234.38	

BP; blood pressure, O2 Sat; Oxygen saturation (medicine), WBC; White blood cells, Lymph; lymphocyte, Neut; Neutrophil, Hb; Hemoglobin, Plt; Platelets, PT; Prothrombin Time, PTT; partial thromboplastin time, INR; International Normalized Ratio, BUN; Blood Urea Nitrogen, Cr; Creatinine, CRP; C-Reactive Protein, ESR; Erythrocyte sedimentation rate, ProBNP; Prohormone brain natriuretic peptide, IL-6; Interleukin-6, Ca Score; calcium score. *Significant at <.05 level. Superscript letters "a" and "b" indicate statistically significant differences between COVID-19 severity groups ($p < 0.05$).

Table 2. Associations between COVID-19 Severity and Comorbidities, Outcomes, and Medication Use in Anticoagulant-Treated Patients

Factors	Category	COVID-19 Severity			p-value
		Mild	Moderate	Sever	
Sex	Female	23 (5.4%)	247 (57.8%)	157 (36.8%)	0.398
	Male	15 (3.5%)	256 (59.7%)	158 (36.8%)	
Hospitalization in ICU	No	36 (4.6%)	499 (63.7%)	248 (31.7%)	<0.001*
	Yes	2 (2.7%)	4 (5.5%)	67 (91.8%)	
Final Outcome Status	No	0 (0.0%)	1 (2.6%)	37 (97.4%)	<0.001*
	Yes	37 (4.6%)	494 (61.2%)	276 (34.2%)	
HTN	No	31 (5.6%)	335 (60.0%)	192 (34.4%)	0.023*
	Yes	7 (2.4%)	167 (56.2%)	123 (41.4%)	
Kidney transplant	No	38 (4.4%)	503 (58.9%)	313 (36.7%)	0.179
	Yes	0 (0.0%)	0 (0.0%)	2 (100%)	
Autoimmune diseases	No	38 (4.4%)	501 (58.7%)	315 (36.9%)	0.495
	Yes	0 (0.0%)	2 (100.0%)	0 (0.0%)	
Mental Disease	No	38 (4.4%)	503 (58.8%)	314 (36.7%)	0.423
	Yes	0 (0.0%)	0 (0.0%)	1 (100%)	

DM	No	30 (5.1%)	348 (58.6%)	216 (36.4%)	0.418
	Yes	8 (3.1%)	155 (59.2%)	99 (37.8%)	
HLP	No	35 (4.6%)	442 (58.1%)	284 (37.3%)	0.487
	Yes	3 (3.2%)	61 (64.2%)	31 (32.6%)	
CAD	No	37 (4.4%)	495 (58.9%)	309 (36.7%)	0.865
	Yes	1 (6.7%)	8 (53.3%)	6 (40.0%)	
COPD, Asthma	No	38 (4.5%)	496 (58.6%)	312 (36.9%)	0.672
	Yes	0 (0.0%)	7 (70.0%)	3 (30.0%)	
CABG	No	38 (4.6%)	486 (58.5%)	307 (36.9%)	0.432
	Yes	0 (0.0%)	17 (68.0%)	8 (32.0%)	
CKD	No	37 (4.4%)	493 (58.9%)	307 (36.7%)	0.86
	Yes	1 (5.3%)	10 (52.6%)	8 (42.1%)	
ESRD	No	38 (4.5%)	500 (58.8%)	312 (36.7%)	0.729
	Yes	0 (0.0%)	3 (50.0%)	3 (50.0%)	
Anemia	No	38 (4.5%)	502 (59.1%)	310 (36.5%)	0.059
	Yes	0 (0.0%)	1 (16.7%)	5 (83.3%)	
Pneumonia	No	38 (4.4%)	502 (58.7%)	315 (36.8%)	0.704
	Yes	0 (0.0%)	1 (100.0%)	0 (0.0%)	
TB	No	38 (4.4%)	501 (58.7%)	315 (36.9%)	0.495
	Yes	0 (0.0%)	2 (100.0%)	0 (0.0%)	
GI Disorder, IBD	No	38 (4.4%)	501 (58.7%)	315 (36.9%)	0.495
	Yes	0 (0.0%)	2 (100.0%)	0 (0.0%)	
RA, AS, SLE, Gout, Sarcoidosis	No	38 (4.5%)	496 (58.6%)	313 (37.0%)	0.475
	Yes	0 (0.0%)	7 (77.8%)	2 (22.2%)	
Migraine, Vertigo	No	38 (4.5%)	499 (58.8%)	312 (36.7%)	0.842
	Yes	0 (0.0%)	4 (57.1%)	3 (42.9%)	
Blood cell malignancies	No	38 (4.5%)	498 (58.6%)	314 (36.9%)	0.46
	Yes	0 (0.0%)	5 (83.3%)	1 (16.7%)	
AWD	No	38 (4.6%)	483 (58.5%)	305 (36.9%)	0.404
	Yes	0 (0.0%)	20 (66.7%)	10 (33.3%)	
Hyperthyroidism	No	38 (4.4%)	502 (58.7%)	315 (36.8%)	0.704
	Yes	0 (0.0%)	1 (100.0%)	0 (0.0%)	
Hypothyroidism	No	35 (4.3%)	472 (58.3%)	302 (37.3%)	0.37
	Yes	3 (6.4%)	31 (66.0%)	13 (27.7%)	
CVA	No	37 (4.5%)	488 (59.4%)	296 (36.1%)	0.09
	Yes	1 (2.9%)	15 (42.9%)	19 (54.3%)	
Brain Damage, SAH, Dementia	No	38 (4.5%)	499 (58.6%)	314 (36.9%)	0.608
	Yes	0 (0.0%)	4 (80.0%)	1 (20.0%)	
Hepatitis B	No	38 (4.4%)	502 (58.7%)	315 (36.8%)	0.704
	Yes	0 (0.0%)	1 (100.0%)	0 (0.0%)	
Seizure	No	38 (4.5%)	495 (58.5%)	313 (37.0%)	0.368
	Yes	0 (0.0%)	8 (80.0%)	2 (20.0%)	
BPH	No	37 (4.4%)	499 (58.7%)	314 (36.9%)	0.251
	Yes	1 (16.7%)	4 (66.7%)	1 (16.7%)	
Cancer, Tumor	No	36 (4.3%)	489 (58.6%)	310 (37.1%)	0.291
	Yes	2 (9.5%)	14 (66.7%)	5 (23.8%)	
Alzheimer's	No	37 (4.3%)	502 (59.0%)	312 (36.7%)	0.092
	Yes	1 (20.0%)	1 (20.0%)	3 (60.0%)	
Parkinson's	No	37 (4.4%)	502 (59.1%)	311 (36.6%)	0.07
	Yes	1 (16.7%)	1 (16.7%)	4 (66.7%)	
IHD	No	28 (4.3%)	391 (59.7%)	236 (36.0%)	0.597
	Yes	10 (5.0%)	112 (55.7%)	79 (39.3%)	
HF	No	38 (4.5%)	490 (58.4%)	311 (37.1%)	0.283
	Yes	0 (0.0%)	13 (76.5%)	4 (23.5%)	
G6PD	No	38 (4.5%)	502 (58.9%)	312 (36.6%)	0.279
	Yes	0 (0.0%)	1 (25.0%)	3 (75.0%)	
Coagulopathy	No	38 (4.5%)	501 (58.7%)	314 (36.8%)	0.916
	Yes	0 (0.0%)	2 (66.7%)	1 (33.3%)	
Heart disease	No	37 (4.3%)	501 (58.9%)	313 (36.8%)	0.217
	Yes	1 (20.0%)	2 (40.0%)	2 (40.0%)	
Ventilation	No	24 (12.7%)	161 (85.2%)	4 (2.1%)	<0.001*
	Yes	14 (2.1%)	332 (50.7%)	309 (47.2%)	
Atorvastatin	No	10 (5.5%)	121 (66.1%)	52 (28.4%)	0.026*
	Yes	28 (4.2%)	380 (56.6%)	263 (39.2%)	
Acetylsalicylic acid (Aspirin)	No	20 (6.6%)	204 (67.3%)	79 (26.1%)	<0.001*
	Yes	18 (3.3%)	297 (53.9%)	236 (42.8%)	
Spironolactone (Aldactone)	No	37 (4.4%)	497 (58.7%)	312 (36.9%)	0.527
	Yes	1 (12.5%)	4 (50.0%)	3 (37.5%)	
Amlodipine and Valsartan	No	38 (4.5%)	501 (58.7%)	314 (36.8%)	0.425
	Yes	0 (0.0%)	0 (0.0%)	1 (100.0%)	
Rosuvastatin	No	38 (4.5%)	500 (58.6%)	315 (36.9%)	0.703
	Yes	0 (0.0%)	1 (100.0%)	0 (0.0%)	
Heparin	No	19 (5.4%)	245 (69.2%)	90 (25.4%)	<0.001*
	Yes	19 (3.8%)	256 (51.2%)	225 (45.0%)	

Warfarin	No	38 (4.5%)	497 (58.5%)	314 (37.0%)	0.606
	Yes	0 (0.0%)	4 (80.0%)	1 (20.0%)	
Non-vitamin K oral anticoagulants (Noac)	No	38 (4.5%)	501 (58.7%)	314 (36.8%)	0.901
	Yes	0 (0.0%)	1 (50.0%)	1 (50.0%)	
Metoclopramide	No	37 (4.3%)	502 (58.8%)	315 (36.9%)	0.006*
	Yes	1 (50.0%)	1 (50.0%)	0 (0.0%)	
Rivaroxaban	No	38 (4.5%)	496 (58.8%)	310 (36.7%)	0.734
	Yes	0 (0.0%)	7 (58.3%)	5 (41.7%)	
Captopril	No	38 (4.5%)	495 (58.9%)	307 (36.5%)	0.426
	Yes	0 (0.0%)	8 (50.0%)	8 (50.0%)	
Losartan	No	38 (4.6%)	497 (59.7%)	297 (35.7%)	<0.001*
	Yes	0 (0.0%)	6 (25.0%)	18 (75.0%)	
Clopidogrel	No	31 (3.9%)	463 (59.0%)	291 (37.1%)	0.068
	Yes	7 (9.9%)	40 (56.3%)	24 (33.8%)	
Furosemide	No	26 (6.5%)	282 (70.9%)	90 (22.6%)	<0.001*
	Yes	12 (2.6%)	221 (48.3%)	225 (49.1%)	
Enoxaparin	No	32 (5.9%)	307 (56.2%)	207 (37.9%)	0.011*
	Yes	6 (1.9%)	196 (63.2%)	108 (34.8%)	
Hydroxychloroquine	No	28 (4.2%)	365 (54.2%)	280 (41.6%)	<0.001*
	Yes	10 (5.5%)	138 (75.4%)	35 (19.1%)	
Troponin	No	18 (3.3%)	304 (55.8%)	223 (40.9%)	0.015*
	Yes	0 (0.0%)	1 (11.1%)	8 (88.9%)	
Thromboembolic lesions	No	34 (4.4%)	457 (58.7%)	288 (37.0%)	0.445
	Yes	0 (0.0%)	13 (54.2%)	11 (45.8%)	
Coronary artery calcification	No	9 (3.2%)	138 (49.8%)	130 (46.9%)	0.876
	Yes	11 (4.1%)	135 (49.8%)	125 (46.1%)	
ECHO	No	32 (4.9%)	395 (60.7%)	224 (34.4%)	0.004*
	Yes	6 (3.5%)	84 (48.6%)	83 (48.0%)	
CT	No	21 (7.8%)	156 (58.2%)	91 (34.0%)	0.008*
	Yes	16 (4.1%)	199 (51.3%)	173 (44.6%)	
ECG	No	4 (15.4%)	16 (61.5%)	6 (23.1%)	0.014*
	Yes	34 (4.2%)	478 (58.4%)	306 (37.4%)	

HTN; Hypertension, DM; Diabetes Mellitus, HLP; hyperlipoproteinemia, CAD; Coronary Artery Disease, COPD; chronic obstructive pulmonary disease, CABG; Coronary Artery Bypass Grafting, CKD; Chronic Kidney Disease, ESRD; End-Stage Renal Disease, TB; Tuberculosis, GI; Gastrointestinal, IBD; Inflammatory bowel disease, RA; Rheumatoid Arthritis, AS; Ankylosing Spondylitis, SLE; Systemic Lupus Erythematosus, AWD; Acute Watery Diarrhoea, CVA; cerebrovascular accident, SAH; subarachnoid hemorrhage, BPH; Benign Prostatic Hyperplasia, IHD; ischemic heart disease, HF; Heart Failure, G6PD; glucose-6-phosphate dehydrogenase, Noac; Non-vitamin K oral anticoagulants (e.g., Apixaban, Dabigatran, Edoxaban, Rivaroxaban), ECHO; Echocardiogram, CT; Computed Tomography, ECG; electrocardiogram. *Significant at <.05 level.

4. Discussion

In our observational study, we examined the clinical outcomes of hospitalized COVID-19 patients who received anticoagulant therapy compared to those who did not. The findings suggest that anticoagulant administration, particularly with low molecular weight heparin (LMWH), was associated with reduced severity of symptoms, lower rates of ICU admission, and decreased mortality. These results are consistent with a growing body of evidence supporting the role of coagulopathy in COVID-19 pathogenesis and the potential therapeutic benefit of anticoagulation.

COVID-19 is now well-recognized as a prothrombotic disease, with elevated risks of VTE, disseminated intravascular coagulation (DIC), and microvascular thrombosis, especially in severe cases [13]. This hypercoagulable state is driven by endothelial injury, cytokine storm, platelet activation, and elevated D-dimer levels, all of which justify early prophylactic or therapeutic anticoagulation [14]. Several clinical studies have demonstrated the beneficial effects of anticoagulants in COVID-19. Tang et al. (2020) found that heparin use in severe cases with coagulopathy significantly reduced 28-day mortality [15]. Similarly, Paranjpe et al. (2020) reported improved survival in hospitalized patients who received systemic anticoagulation, particularly among those on mechanical ventilation [9]. A multicenter study by Nadkarni et al. (2020) also confirmed lower in-hospital mortality in patients receiving both prophylactic and therapeutic anticoagulants [10]. Moreover, Llitjos et al. (2020) observed a high incidence of thromboembolic events in ICU patients despite standard prophylaxis, suggesting the need for more aggressive anticoagulant strategies in critical cases [16]. Helms et al. (2020) also documented a markedly increased prevalence of pulmonary embolism among COVID-19 patients in the ICU, further reinforcing the role of thromboprophylaxis [17].

However, the optimal dose and timing of anticoagulation remain debated. The randomized ACTION trial found no benefit of therapeutic-dose anticoagulation over prophylactic dosing in patients with elevated D-dimer levels, with increased bleeding risk in the therapeutic group [8]. Conversely, the multiplatform ATTACC, ACTIV-4a, and REMAP-CAP trials showed that therapeutic-dose heparin in moderately ill patients improved survival and reduced organ support requirements, although this benefit was not observed in critically ill patients [18]. Additionally, a systematic review by Jiménez et al. (2021) confirmed that although anticoagulation reduces thrombotic events, it also increases bleeding complications, highlighting the importance of individualized therapy [19].

Another meta-analysis by Spyropoulos et al. (2021) supported intermediate or full-dose anticoagulation in select high-risk patients with elevated D-dimer and no contraindications [20]. Similar to the Tessema et al. (2023), our findings confirm that anticoagulant therapy plays a vital role in managing hospitalized COVID-19 patients [12]. While the Ethiopian cohort revealed a higher mortality rate in patients receiving therapeutic doses, particularly among critically ill patients, our study showed a beneficial effect of anticoagulant therapy in reducing symptom severity and improving outcomes, without a significant increase in bleeding events [12]. This contrast may stem from differences in patient populations, sample sizes, or underlying comorbidities. Taken together, these findings suggest that anticoagulant therapy, when carefully applied based on clinical and laboratory indicators, can improve outcomes in hospitalized COVID-19 patients. Our study adds to this growing evidence, showing that anticoagulants may reduce disease progression and severity. Nonetheless, future randomized trials are needed to refine protocols, determine ideal candidates, and minimize adverse effects. This retrospective single-center study is limited by potential biases inherent to medical record review, including incomplete documentation and lack of randomization. The heterogeneity of anticoagulant types and dosing regimens may have influenced outcomes. Additionally, long-term post-discharge events were not assessed, which limits the evaluation of delayed complications.

In conclusion, anticoagulant therapy appears to be a beneficial adjunctive treatment in hospitalized COVID-19 patients, particularly for those with elevated coagulation markers or at high risk of thromboembolic complications. Our findings suggest that the use of anticoagulants, especially LMWH, may reduce the severity of symptoms and improve overall clinical outcomes. However, careful consideration of individual risk factors, including bleeding risk, is essential. Given the evolving nature of COVID-19 and its complications, further large-scale, randomized clinical trials are warranted to establish optimal dosing, timing, and duration of anticoagulant therapy in diverse patient populations. Such studies will help to refine current treatment guidelines and improve patient prognosis.

Authors' contributions

Conceptualization and design of the study; IJ and RP, Data collection and acquisition; IJ, NZA, MB, MTHG, SA, MS, KA, FJ, RP. Analysis and interpretation of data: HS, Drafting of the manuscript: RP, Critical revision of the manuscript for important intellectual content: SA, RP. All authors approved the final version of article.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

Ethical approval was obtained from the Babol University of Medical Sciences, with the approval code IR. MUBABOL.REC.1399.412. Written informed consent was obtained from all participants or their legal guardians. Patient data were anonymized to ensure confidentiality, and all efforts were made to protect the privacy and rights of the study participants.

Financial support

This project has received a grant from Babol University of Medical Sciences with tracking code 724133278.

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