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Association of anticoagulant therapy dosing with laboratory biomarkers and clinical outcomes in critically ill COVID-19 patients in the ICU

Povezanost doziranja antikoagulantne terapije sa laboratorijskim biomarkerima i kliničkim ishodima kod kritično obolelih od COVID-19 u odeljenju intenzivne nege

Igor Vasković*†, Marija Marković*†, Ljiljana Arsenović‡, Aleksandra Ignjatović§, Mihailo Stojić*, Vojislava Nešković*†

Military Medical Academy, *Clinic for Anesthesiology and Intensive Care, ‡Institute for Medical Biochemistry, Belgrade, Serbia; †University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; §University of Niš, Faculty of Medicine, Department of Medical Statistics and Informatics, Niš, Serbia

Abstract

Background/Aim. In immunothrombotic disorders such as coronavirus disease 2019 (COVID-19), D-dimer levels are frequently elevated, reflecting increased fibrin formation and turnover. Additional biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) and levels of C-reactive protein (CRP), and lactate dehydrogenase (LDH), are associated with disease severity and outcomes. The aim of the study was to evaluate the impact of two different anticoagulation protocols on serum levels of biomarkers D-dimer, NLR, CRP, and LDH, as well as their prognostic value regarding clinical outcomes in critically ill patients with COVID-19. **Methods.** The retrospective study included critically ill COVID-19 patients, admitted to the Intensive Care Unit (ICU) between April 2020 and December 2021, and compared D-dimer–guided and anti-Xa–guided anticoagulation protocols. Patients were divided into two groups according to the anticoagulant therapy regimen: a group with a protocol guided by anti-Xa values (AXa group – A-XaG) and a group with a protocol dosing according to D-dimer values (D-d group – D-dG). **Results.** A total of 395 patients were analyzed: 137 in A-XaG and 258 in D-dG. The levels of CRP, LDH, and D-dimer were significantly lower in A-XaG compared to D-dG ($p < 0.001$, $p < 0.001$, and $p = 0.001$, respectively). The univariate analysis identified age [odds ratio (OR): 1.064; $p < 0.001$], LDH (OR: 1.002; $p < 0.001$), CRP (OR: 1.005; $p < 0.001$), and D-dimer (OR: 1.054; $p = 0.020$) as prognostic factors for mortality. The multivariate model analysis revealed that only age > 64 years (OR: 10.215; $p < 0.001$) and LDH > 395 U/L (OR: 5.491; $p = 0.005$) remained independently associated with mortality. **Conclusion.** Anti-Xa–guided anticoagulation was associated with lower inflammatory biomarker levels in ICU COVID-19 patients. While univariate analysis identified age, LDH, CRP, and D-dimer as potential prognostic factors for mortality, only age and LDH remained significant in multivariate modelling, suggesting independent prognostic value in this patient population.

Keywords:
anticoagulants; biomarkers; covid-19; factor xa; heparin; intensive care units; prognosis.

Apstrakt

Uvod/Cilj. Kod imunotrombotskih poremećaja kao što je bolest izazvana korona virusom 2019 (*coronavirus disease* 2019–COVID-19), nivoi D-dimera često su povišeni, što odražava povećano stvaranje i razgradnju fibrina. Dodatni biomarkeri, kao što su odnos neutrofila i limfocita (*neutrophil-to-lymphocyte ratio* – NLR) i nivoi C-reaktivnog proteina (CRP) i laktat dehidrogenaze (LDH), povezani su sa težinom i ishodima bolesti. Cilj rada bio je da se proceni uticaj dva različita antikoagulaciona protokola na nivoe biomarkera D-dimer, NLR, CRP i LDH u serumu, kao i njihova prognostička vrednost u pogledu kliničkih ishoda kod kritično obolelih od COVID-19. **Metode**. Retrospektivnom studijom obuhvaćeni su kritično oboleli od COVID-19, primljeni na Odeljenje intenzivne nege u periodu od aprila 2020. do decembra 2021. godine i upoređeni su protokoli za vođenje antikoagulantne terapije pomoću D-dimera i pomoću anti-Xa inhibitora. Bolesnici su prema režimu antikoagulantne terapije bili podeljeni u dve

Correspondence to: Igor Vasković, Military Medical Academy, Clinic for Anesthesiology and Intensive Care, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: vaske79@gmail.com

grupe: grupu u kojoj je primenjen protokol vođen anti-Xa vrednostima (AXa grupa – A-XaG) i grupu gde je primenjen protokol sa doziranjem prema D-dimer vrednostima (D-d grupa – D-dG). **Rezultati**. Analizirano je ukupno 395 bolesnika: 137 u A-XaG i 258 u D-dG. Vrednosti CRP, LDH i D-dimera bile su značajno niže u A-XaG u odnosu na D-dG ($p < 0,001$, $p < 0,001$, $p = 0,001$, redom). Univarijantnom analizom su kao prognostički faktori mortaliteta pokazani životno doba [*odds ratio* (OR): 1,064; $p < 0,001$)], LDH (OR: 1,002; $p < 0,001$), CRP (OR: 1,005; $p < 0,001$) i D-dimer (OR: 1,054; $p = 0,020$). Analizom multivarijantnog modela pokazano je da su samo životno doba > 64 godine (OR: 10,215; $p < 0,001$) i LDH > 395 U/L (OR: 5,491; $p = 0,005$) ostali nezavisno povezani sa smrtnim ishodom. **Zaključak.** Antikoagulantna terapija vođena anti-Xa vrednostima bila je povezana sa nižim vrednostima inflamacijskih biomarkera kod obolelih od COVID-19 na Odeljenju intenzivne nege. Iako su univarijantnom analizom kao potencijalni prognostički faktori mortaliteta identifikovani životno doba, LDH, CRP i D-dimer, samo su životno doba i LDH ostali statistički značajni pokazatelji u multivarijantnom modelu, što ukazuje na nezavisnu prognostičku vrednost kod te populacije bolesnika.

Ključne reči:
antikoagulansi; biomarkeri; covid-19; faktor xa; heparin; intenzivna nega, odeljenja; prognoza.

Introduction

Severe coronavirus disease 2019 (COVID-19) with pulmonary involvement is characterized by hypercoagulability and elevated systemic inflammatory activation. Pulmonary vascular injury and microthrombosis are increasingly recognized as central features of this inflammation-coagulation interplay, referred to as immunothrombosis [1, 2]. COVID-19–associated coagulopathy is largely driven by immunothrombosis, in which inflammatory activation of endothelial cells, monocytes, platelets, and leukocytes promotes tissue factor expression, thrombin generation, and fibrin deposition, particularly within the pulmonary microvasculature. In addition, activated neutrophils release neutrophil extracellular traps, which provide a procoagulant surface, further enhancing thrombin generation and platelet activation. Together, these mechanisms contribute to the immunothrombotic phenotype observed in severe COVID-19 cases [3]. Some conceptual models describe severe COVID-19 as a stage-dependent process in which early disease is characterized by high fibrinogen, Von Willebrand factor, and P-selectin levels with normal or only slightly increased D-dimer, whereas disease progression is associated with rapidly rising D-dimer levels, depletion of some coagulation-related biomarkers, and later cytokine storm, indicating poor prognosis [4].

Given this interplay, several biomarkers that can be readily assessed through routine laboratory testing have been identified as indicators of disease progression and mortality [3]. These biomarkers include the neutrophil-to-lymphocyte ratio (NLR) as an independent prognostic factor linked to worse outcomes in COVID-19 patients [5, 6]. Additionally, levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH) have been shown to correlate with the severity of COVID-19, providing further insights into the inflammatory and tissue damage processes [7, 8]. This growing body of evidence underscores the potential of these biomarkers as valuable tools for risk stratification and management in clinical practice [8]. Elevated D-dimer levels predict in-hospital mortality, indicate an increased risk of a procoagulant state, and are associated with an increased risk of thromboembolic complications [9, 10]. Conversely, the safety profiles and effectiveness of various anticoagulation strategies in critically ill patients with COVID-19 remain inadequately understood. This is particularly relevant when considering the multifaceted properties of heparin, highlighting the need for further research [11].

In a previous study conducted in the same cohort of critically ill COVID-19 patients, we demonstrated that anticoagulation tailored according to anti-Xa activity was associated with improved survival compared with D-dimer–guided anticoagulation. Specifically, the anti-Xa–guided strategy was linked to lower observed mortality and a reduced incidence of thromboembolic complications, without an increase in bleeding events. These findings suggested that anti-Xa–guided anticoagulation may offer advantages over D-dimer–based dose adjustment alone [12].

Building on these observations, the present study investigated whether anti-Xa–guided anticoagulation is associated with differences in inflammatory and coagulation biomarker dynamics compared with a D-dimer–guided strategy in critically ill patients with COVID-19, and whether these biomarkers have prognostic value for clinical outcomes.

We hypothesized that anti-Xa–guided anticoagulation, which more accurately reflects the achieved anticoagulant effect of low-molecular-weight heparin (LMWH), would be associated with different inflammatory and coagulation biomarker profiles compared with D-dimer–guided anticoagulation in critically ill COVID-19 patients. We further hypothesized that routinely available admission biomarkers (including NLR, CRP, LDH, and D-dimer) would have prognostic value for clinical outcomes.

Accordingly, the primary aim of the study was to analyze the association of two different anticoagulation protocols with inflammatory biomarker levels. The secondary aim was to assess the prognostic capacity of biomarkers for mortality.

Methods

Study design

This retrospective observational study examined patients with COVID-19, confirmed by laboratory testing, admitted to the Intensive Care Unit (ICU) at the specialized COVID-19 Hospital in Karaburma, Belgrade, Serbia, from April 2020 to

December 2021. The study was approved by the Ethics Committee of the Military Medical Academy (No. 19/2022, from May 25, 2022). This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Data from medical records were analyzed anonymously.

The study included patients aged 18 years and older, of both sexes, who tested positive for COVID-19 and showed signs of respiratory failure.

Patients were excluded from the study if they met any of the following criteria: admission to the ICU for less than 24 hrs, transfer from another ICU setting, or lack of complete anticoagulant therapy data during their treatment course.

Respiratory failure was defined by $SpO_2 < 90\%$ at ICU admission; according to institutional practice, these patients received escalation of respiratory support, including high-flow nasal cannula, noninvasive ventilation, or invasive mechanical ventilation. Patients initially receiving low-flow oxygen support (*via* nasal cannula or oxygen mask) with $SpO_2 < 94\%$, a respiratory rate $\geq$ 25/min, and $pO_2 < 65$ mmHg were also included if they demonstrated rapid clinical and radiological deterioration and subsequently underwent escalation of respiratory support.

Anticoagulation protocols were followed according to local guidelines. Initially, anticoagulation at our institution was guided by D-dimer levels. The threshold of 2 mg/L fibrinogen equivalent units (FEU) reflected the institutional anticoagulation protocol in place at the time of patient enrollment (more than four times the normal upper limit). However, following the admission of 270 patients and in response to the high incidence of thrombotic events and observed variability in heparin responsiveness, the institutional protocol was revised to incorporate anti-Xa–guided dose adjustments. This modification was introduced to assess the achieved anticoagulant effect of LMWH and to guide anticoagulation intensity.

Because the anticoagulation protocols were implemented sequentially during different phases of the pandemic, group allocation was determined by the institutional protocol in place at the time of ICU admission. Accordingly, the study represents a protocol-based observational comparison, not a randomized group allocation. Patient medical records were reviewed, highlighting demographics, treatment interventions, and laboratory and hemostatic parameters. Peripheral venous blood samples were collected for laboratory analysis, using ethylenediaminetetraacetic acid-anticoagulated whole blood for complete blood count assessments *via* the fully automated ADVIA 120 system. Hemostasis parameters were evaluated from citrated plasma obtained after centrifugation of whole blood at 3,000 g for 10 min. Quantification was conducted on a Siemens BCS analyzer under standardized analytical conditions. D-dimer was measured using a latex immunoturbidimetric assay, while LMWH anti-Xa activity was determined using a chromogenic spectrophotometric method in accordance with the manufacturer's instructions. All assays were performed using the same analyzer and methodology throughout the study period, ensuring analytical consistency.

Patients were stratified into two cohorts according to the anticoagulation protocol (Table 1): a D-dimer–guided group (D-dG) and an anti-Xa–guided group (A-XaG).

The first group – D-dG received nadroparin according to the prescribed protocol. Patients weighing 100 kg or less were given nadroparin at a dose of 86 U AXa/kg body weight (BW), administered subcutaneously (sc) once daily. Those exceeding 100 kg were administered 8,550 U AXa daily, provided their D-dimer levels were at or below 2 mg/L FEU. For patients with D-dimer levels higher than 2 mg/L FEU, LMWH was prescribed sc twice daily based on their BW: nadroparin 86 U AXa/kg BW sc twice daily for those weighing $\leq$ 100 kg, and nadroparin 8,550 U AXa twice daily for those over 100 kg (Table 1).

In the D-dimer–guided protocol, patients were stratified according to a threshold of 2 mg/L FEU, which corresponds to approximately 4 times the upper limit of normal in our laboratory. This threshold reflected the institutional anticoagulation protocol in place during the early phase of the pandemic and was selected as a pragmatic marker of increased thrombotic risk based on contemporaneous evidence linking elevated D-dimer levels with poor outcomes in COVID-19. Patients with D-dimer levels $\leq$ 2 mg/L received prophylactic-intensity anticoagulation, whereas those with levels > 2 mg/L received therapeutic-intensity LMWH. Thus, the division of

Table 1

Anti-Xa–guided and D-dimer–guided anticoagulation dosing protocols

Therapeutic protocol	Nadroparin dose
D-dimer	
≤ 2 mg/L FEU	
BW ≤ 100 kg	86 U AXa/kg OD
BW > 100 kg	8,550 U AXa OD
> 2 mg/L FEU	
BW ≤ 100 kg	86 U AXa/kg TD
BW > 100 kg	8,550 U AXa TD
Anti-Xa, U/mL	
< 0.35	increased by 25%
0.36–0.49	increased by 10%
1.1–1.5	decrease by 20%
1.6–2.0	decrease by 30%
> 2.0	decrease by 40% and postpone the next dose until anti-Xa is < 0.5

FEU – fibrinogen equivalent units; BW – body weight; OD – once daily; TD – twice daily.
***Note*: Target anti-Xa level was set between 0.5 U/mL and 1.0 U/mL due to concerns regarding hypercoagulability in COVID-19 patients.**

D-dG reflected prospective routine clinical practice rather than a *post hoc* analytical subdivision. D-dimer was used as a marker of thromboinflammatory activity and risk stratification, not as a diagnostic test for macrothrombosis; patients with clinically suspected or confirmed thromboembolic events were managed according to standard diagnostic and therapeutic pathways independent of protocol allocation.

The second group – A-XaG received weight-adjusted nadroparin with twice a day dosing guided by anti-Xa levels to achieve the desired therapeutic anticoagulation. Anti-Xa peak levels were monitored once the drug concentration stabilized: 4 hrs post-morning dose and after four doses of LMWH treatment. If the anti-Xa level fell below 0.35 U/mL, the dosage was increased by 25%. For levels between 0.36 and 0.49 U/mL, the dosage was raised by 10%. The target anti-Xa level was set between 0.5 U/mL and 1.0 U/mL due to concerns regarding hypercoagulability in COVID-19 patients. If the anti-Xa level exceeded 1.0 U/mL, the dosage was decreased according to the anti-Xa-based protocol (Table 1).

Since nadroparin is available in fixed prefilled syringe strengths, dose adjustments were implemented as clinically practical approximations using the nearest available syringe strength or adjusted injection volume. After each dose adjustment, peak anti-Xa activity was rechecked at steady state (4 hrs after the morning dose) to confirm the change toward the target range and to avoid overdosing.

Additional methodological details have been reported previously [12].

Statistical analysis

The statistical analyses for this study were performed using R software, version 4.3.0. The data are presented using standard descriptive statistics, including means, standard deviations, medians with interquartile ranges, and counts and percentages as appropriate. Data normality was assessed using the Kolmogorov-Smirnov test. Group comparisons of numerical data were performed using a *t*-test or the Mann-Whitney test, depending on the data distribution. Comparisons of numerical data between two measurements were conducted using a paired *t*-test or a Wilcoxon test, depending on the data distribution. Categorical data analysis employed the Chi-squared test or Fisher's exact test. Univariate and multivariate logistic regression analyses were used to estimate the association between a fatal outcome, the dependent variable, and one or more independent variables. Prognostic modelling was performed in the overall cohort to evaluate associations between admission biomarkers and clinical outcomes (survival vs. non-survival); it was not designed to assess prognostic performance separately within each anticoagulation protocol. A receiver operating characteristic (ROC) curve was used to estimate the discriminative ability of inflammation markers and determine the cut-off value for specific variables.

Multiple comparisons were controlled by adjusting all *p*-values using the Benjamini-Hochberg correction to control the false discovery rate. For clarity and transparency, both unadjusted and false discovery rate-adjusted *p*-values were reported. The statistical significance level was set at $p < 0.05$.

Results

Baseline demographic characteristics did not differ significantly between the two groups with respect to age or sex. The mean age was 66.31 years in A-XaG and 68.01 years in D-dG ($p = 0.253$). Comorbidities were generally similar between groups; however, hypertension was more frequent in A-XaG, with borderline significance ($p = 0.050$) (Table 2).

Table 2

Demographic and clinical characteristics of the population according to the two treatment groups

Variable	Group		*p*-value[a]
	A-XaG (n = 137)	D-dG (n = 258)	
Gender			
male	106 (77.0)	193 (74.8)	0.658
female	31 (22.6)	65 (25.5)	
Age, years	66.31 ± 13.39	68.01 ± 14.33	0.253[b]
Comorbidity	108 (78.8)	193 (74.8)	0.441
diabetes mellitus type I	28 (20.4)	54 (21.3)	0.952
diabetes mellitus type II	2 (1.5)	8 (3.2)	0.505
hypertension	84 (61.3)	128 (50.4)	0.050
cardiovascular diseases	27 (19.7)	68 (27.0)	0.141
respiratory diseases	14 (10.2)	18 (7.1)	0.389
malignancy	5 (3.6)	10 (4.0)	1.000
chronic kidney failure	2 (1.5)	10 (4.0)	0.228
other	40 (29.2)	72 (27.9)	0.878
Medications			
Aspirin®, clopidogrel	16 (11.7)	50 (19.4)	0.070
tocilizumab	63 (46.0)	48 (18.6)	< 0.001
dexamethasone	122 (89.1)	182 (70.5)	< 0.001

A-XaG – anti-Xa group; D-dG – D dimer group; n – number of patients.
All values are given as numbers (percentages) or mean ± standard deviation.
***Note*: [a] Chi-squared test; [b] independent *t*-test.**

Table 3

Laboratory parameters for the two treatment groups at admission and the final measurement

Parameter*	Admission	Final measurement†	*p*-value
Leukocytes			
A-XaG	8.44 (6.56–11.40)	9.95 (7.07–14.67)	0.001/**0.003**[c]
D-dG	8.56 (5.74–11.71)	10.82 (7.50–15.14)	< 0.001/< **0.001**[c]
p-value	0.680/**0.711**[b]	0.320/**0.367**[b]	
Neutrophils			
A-XaG	7.50 (5.55–10.45)	8.00 (5.05–13.40)	0.023/**0.037**[c]
D-dG	7.55 (4.80–10.30)	9.65 (5.92–14.00)	< 0.001/< **0.001**[c]
p-value	0.719/**0.719**[b]	0.095/**0.127**[b]	
Lymphocytes			
A-XaG	0.60 (0.40–0.80)	0.70 (0.40–1.20)	< 0.001/< **0.001**[c]
D-dG	0.60 (0.40–0.90)	0.70 (0.40–1.10)	< 0.001/< **0.001**[c]
p-value	0.398/**0.443**[b]	0.238/**0.287**[b]	
Hemoglobin‡			
A-XaG	134.02 ± 18.24	126.61 ± 19.96	< 0.001/< **0.001**[ad]
D-dG	128.06 ± 17.99	122.45 ± 18.59	< 0.001/< **0.001**[d]
p-value	0.002/**0.002**[a]	0.048/**0.069**[a]	
Platelets			
A-XaG	228.00 (167.50–287.00)	213.00 (148.00–283.50)	0.268/**0.318**[c]
D-dG	227.00 (169.00–303.00)	256.50 (169.50–353.50)	0.015/**0.025**[c]
p-value	0.432/**0.465**[b]	0.002/**0.004**[b]	
IL-6			
A-XaG	81.8 (39.6–156.4)		
D-dG	58 (25.2–116.0)		
p-value	0.121/**0.157**[b]		

A-XaG – anti-Xa group; D-dG – D dimer group; IL – interleukin.
***Note*: anti-Xa vs. D-dimer group ([a] independent *t*-test or [b] Mann-Whitney test), admission vs. final measurement ([c] Wilcoxon test/ [d] paired *t*-test); * non-normally distributed data are presented as median (interquartile range) and ‡ normally distributed data are presented as mean ± standard deviation; *p*-values are presented as unadjusted or Benjamini-Hochberg adjusted (adjusted *p*-values are shown in bold); † final measurement refers to the last recorded value prior to death or discharge.**

Reference ranges: leukocytes 4.0–11.0 × 10^9/L, neutrophils 1.9–8.0 × 10^9/L, lymphocytes 0.9–5.2 × 10^9/L, hemoglobin 130–180 g/L, platelets 160–370 × 10^9/L, and IL-6 1.5–7 pg/mL.

Immunomodulatory therapy was administered more frequently in A-XaG compared to D-dG (tocilizumab: 46.0% vs. 18.6%, $p < 0.001$; dexamethasone: 89.1% vs. 70.5%, $p < 0.001$). Antiplatelet therapy was used in 16 (11.7%) patients in A-XaG and 50 (19.4%) patients in D-dG, with no significant difference between groups ($p = 0.070$) (Table 2).

Changes in biomarker levels during follow-up differed between anticoagulation strategies. Table 3 and Figure 1 summarize laboratory parameters for both patient groups at admission and at the final measurement (last measurement at the time of death or discharge from the ICU). At admission, NLR, D-dimer, and LDH values did not differ significantly between groups. At the final measurement, A-XaG demonstrated significantly lower CRP, LDH, and D-dimer levels ($p < 0.001$, $p < 0.001$, and $p = 0.001$, respectively), with no significant difference in NLR between the groups (Figure 1).

When admission values were compared with final measurements, NLR and D-dimer levels increased significantly in D-dG ($p < 0.001$ for both), while LDH levels did not change significantly ($p = 0.326$). In contrast, CRP levels decreased significantly during follow-up ($p < 0.001$). In A-XaG, LDH and CRP levels decreased significantly over time ($p < 0.001$ for both), while D-dimer and NLR levels remained stable ($p = 0.662$ and $p = 0.376$, respectively) (Figure 1).

After applying the Benjamini-Hochberg correction, all previously significant *p*-values remained significant, except for the hemoglobin levels between groups at the final measurement, which was no longer significant (adjusted $p = 0.069$) (Table 3).

Analysis of mortality risk in the overall studied cohort

Mortality analyses were performed in the overall cohort independent of anticoagulation protocol allocation.

Demographic parameters based on clinical outcomes

The analysis revealed no significant differences in survival rates between male and female cohorts. However, it was noted that the cohort of deceased patients had a significantly higher average age compared to the survivors ($p < 0.001$), as presented in Table 4.

Laboratory parameters at admission and final measurement based on clinical outcomes

The laboratory parameters at admission that were significantly higher in non-survivors included leukocyte count

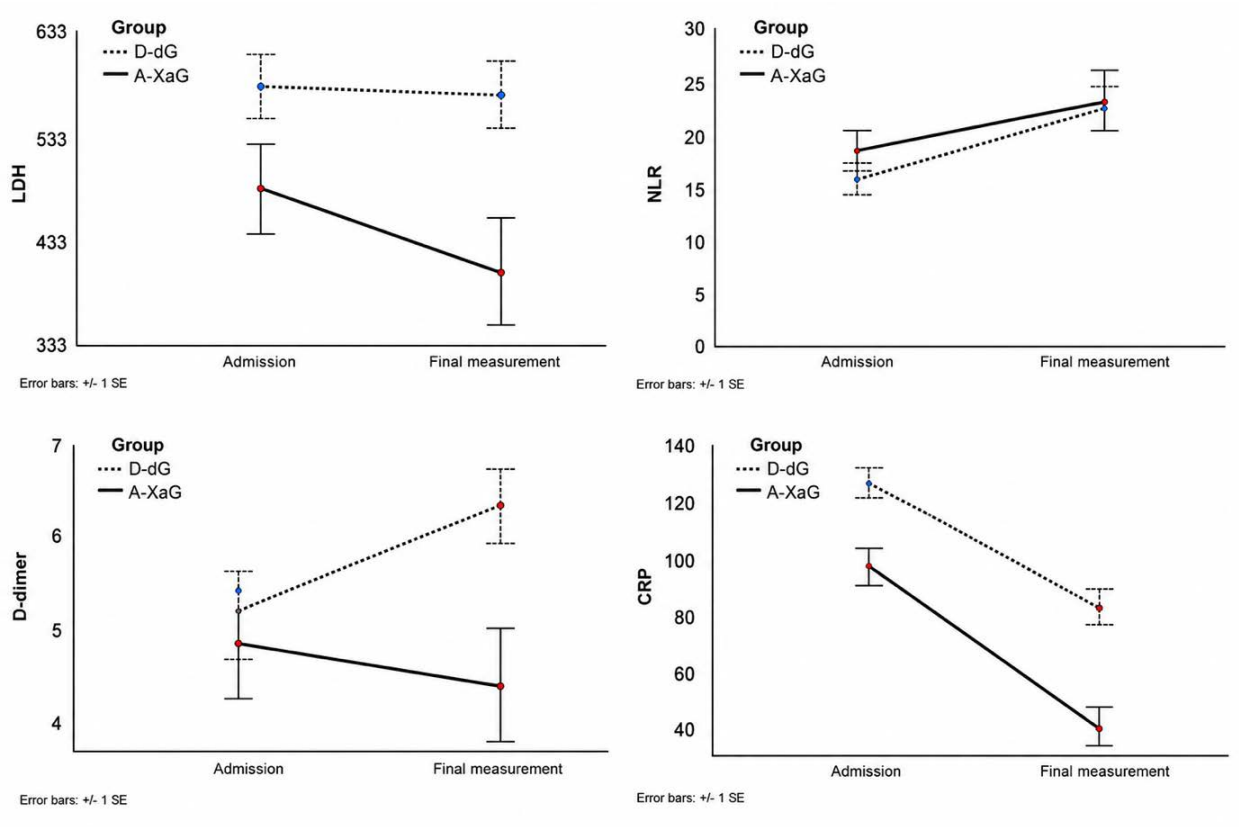


Fig. 1 – Changes in inflammatory and coagulation biomarkers in the D-dimer–guided and anti-Xa–guided anticoagulation groups at admission and at the final measurement (death or Intensive Care Unit discharge). Error bars represent ± 1 standard error (SE) of the mean. A-XaG – anti-Xa group; D-dG – D dimer group; LDH – lactate dehydrogenase; NLR – neutrophil-to-lymphocyte ratio; CRP – C-reactive protein.

Table 4

Demographic parameters based on clinical outcomes

Parameter	Survivors	Non-survivors	*p*-value[a]
Male	161 (78.9)	138 (72.3)	0.122/**0.158**
Female	43 (21.1)	53 (27.7)	
Age	62.39 ± 13.63	72.82 ± 12.33	< 0.001/< **0.001**[b]

All values are given as numbers (percentages) or mean ± standard deviation.
***Note*: [a] Chi-squared test, [b] independent *t*-test; *p*-values are presented as unadjusted or Benjamini-Hochberg adjusted (adjusted *p*-values are shown in bold).**

(p = 0.038), neutrophil count (p = 0.019), NLR (p < 0.001), LDH (p < 0.001), CRP (p = 0.001), D-dimer (p = 0.001), and IL-6 levels (p = 0.001) (Table 5). At the time of the final measurement, non-survivors continued to show significantly higher levels of leukocyte count (p < 0.001), neutrophil count (p < 0.001), NLR (p < 0.001), LDH (p < 0.001), CRP (p < 0.001), and D-dimer levels (p < 0.001) (Table 5).

All previously significant *p*-values remained significant after Benjamini-Hochberg correction, except for the following: leukocyte count between survivors and non-survivors (adjusted p = 0.057), D-dimer levels between admission and final measurements among survivors (adjusted p = 0.070), and LDH values between admission and final measurements among non-survivors (adjusted p = 0.052) (Table 5).

Univariate and multivariate logistic regression analysis for mortality risk assessment

In the univariate analysis, significant prognostic factors for mortality were age [odds ratio (OR): 1.064, 95% confidence interval (CI): 1.045–1.083, p < 0.001], LDH (OR: 1.002, 95% CI: 1.001–1.003, p < 0.001), CRP (OR: 1.005, 95% CI: 1.002–1.008, p < 0.001), and D-dimer (OR: 1.054, 95% CI: 1.009–1.102, p = 0.020) (Table 6). In multivariate model 1, age (OR: 1.085, 95% CI: 1.032–1.140, p = 0.001) and LDH (OR: 1.003, 95% CI: 1.000–1.006, p = 0.024) showed the most consistent independent associations with mortality (Table 6). ROC curve analysis demonstrated good discriminative ability of LDH at admission for a fatal

Table 5

Laboratory parameters based on clinical outcomes

Parameter *	Admission	Final measurement†	*p*-value
Leukocytes			
survivors	8.27 (5.68–10.64)	8.09 (5.98–10.72)	0.703/**0.719** [c]
non–survivors	8.90 (6.54–12.54)	14.27 (10.89–18.99)	< 0.001/< **0.001** [c]
p-value[a]	0.038/**0.057** [b]	< 0.001/< **0.001** [b]	
Neutrophils			
survivors	7.15 (4.50–9.35)	6.25 (4.40–9.10)	0.146/**0.183** [c]
non–survivors	7.82 (5.60–11.50)	13.00 (9.75–17.30)	< 0.001/< **0.001** [c]
p-value[a]	0.019/**0.031** [b]	< 0.001/< **0.001** [b]	
Lymphocytes			
survivors	0.60 (0.50–0.90)	1.00 (0.70–1.40)	< 0.001/**0.001** [c]
non–survivors	0.60 (0.40–0.80)	0.40 (0.30–0.70)	0.001/**0.001** [c]
p-value[a]	0.012/**0.020** [b]	< 0.001/< **0.001** [b]	
NLR			
survivors	9.17 (5.83–16.23)	6.12 (3.39–10.72)	< 0.001/< **0.001** [c]
non–survivors	14.00 (7.17–24.73)	29.00 (17.00–44.03)	< 0.001/< **0.001** [c]
p-value[a]	< 0.001/**0.001**	< 0.001/< **0.001**	
Hemoglobin‡			
survivors	131.39 ± 18.78	128.22 ± 16.44	< 0.001/< **0.001** [ad]
non–survivors	128.80 ± 17.66	119.05 ± 20.91	< 0.001/< **0.001** [d]
p-value[a]	0.123/**0.157**	< 0.001/< **0.001**	
Platelets			
survivors	240.00 (184.00–321.00)	281.00 (199.75–383.00)	< 0.001/< **0.001** [c]
non–survivors	214.00 (159.50–285.50)	185.00 (133.00–256.00)	0.003/**0.006** [c]
p-value[a]	0.003/**0.006** [b]	< 0.001/< **0.001** [b]	
LDH			
survivors	380.50 (282.75–521.75)	293.00 (219.00–379.00)	< 0.001/< **0.001** [c]
non–survivors	526.00 (416.25–742.25)	544.00 (413.00–810.25)	0.034/**0.052** [c]
p-value[a]	< 0.001/< **0.001** [b]	< 0.001/< **0.001** [b]	
CRP			
survivors	90.30 (43.50–148.10)	12.50 (2.82–34.50)	< 0.001/< **0.001** [c]
non–survivors	128.00 (58.87–189.60)	79.30 (28.15–187.10)	0.002/**0.004** [c]
p-value[a]	0.001/**0.001** [b]	< 0.001/< **0.001** [b]	
D-dimer			
survivors	1.64 (0.96–4.07)	1.12 (0.64–3.96)	0.050/**0.070** [c]
non–survivors	2.93 (1.22–8.76)	4.04 (2.20–10.92)	< 0.001/< **0.001** [c]
p-value[a]	0.001/**0.001** [b]	< 0.001/< **0.001** [b]	
IL–6			
survivors	46.79 (19.88–108.87)		
non–survivors	107.25 (58.60–184.98)		
p-value[a]	0.001/**0.003** [b]		

NLR – neutrophil-to-lymphocyte ratio; LDH – lactate dehydrogenase; CRP – C-reactive protein; IL – interleukin.

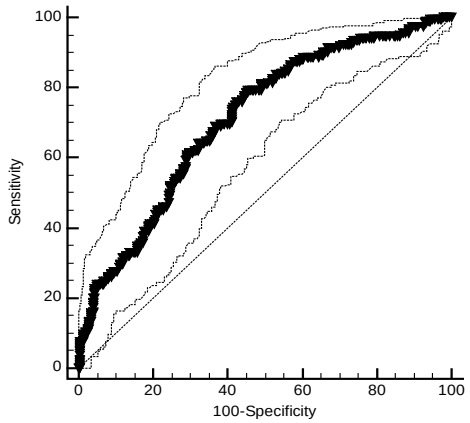
***Note*: survivors vs. non-survivors ([a] independent *t*-test or [b] Mann-Whitney test), admission vs. final measurement ([c] Wilcoxon test/ [d] paired *t*-test); * non-normally distributed data are presented as median (interquartile range); ‡normally distributed data are presented as mean ± standard deviation; *p*-values are presented as unadjusted or Benjamini-Hochberg adjusted (adjusted *p*-values are shown in bold); † final measurement refers to the last recorded value prior to death or discharge.**

Reference ranges: LDH 84–246 U/L, CRP < 10 mg/L, D-dimer 0.22–0.45 mg/L fibrinogen equivalent units (FEU). For other reference ranges, see Table 3.

outcome (area under the curve – AUC: 0.708, $p < 0.001$), with a cut-off value > 395 U/L (Figure 2). Multivariate model 2, built based on LDH cut-off value and age, showed that age > 64 years (OR: 10.215, 95% CI: 3.160–33.021, $p < 0.001$) and LDH > 395 U/L (OR: 5.491, 95% CI: 1.657–18.199, $p = 0.005$) were significantly associated with fatal outcomes (Table 6).

Exploratory subgroup analyses

These analyses were exploratory and are presented for descriptive purposes. Within the D-dimer–guided anticoagulation group, 42 (16.3%) patients had D-dimer levels < 2 mg/L and, therefore, received prophylactic anticoagulation, whereas the majority of patients (83.7%) had D-dimer levels



AUC	0.708
Standard error[a]	0.026
95% CI[b]	0.660–0.753
p-value	< 0.001
Youden index J	0.338
95% CI[a]	0.242–0.412
Associated criterion	> 395
95% CI[a]	> 326–> 441
Sensitivity	79.35
Specificity	54.46

Fig. 2 – Receiver operating characteristic curve analysis of lactate dehydrogenase at admission. AUC – area under the curve; CI – confidence interval.
***Note*: [a] DeLong method, [b] Binomial exact method.**

Table 6

Association of biomarkers at admission with fatal outcomes in logistic regression models

Parameter	Univariate			Multivariate					
				model 1			model 2		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age*	1.064	1.045–1.083	< 0.001	1.085	1.032–1.140	0.001	10.215	3.160–33.021	< 0.001
Sex	1.438	0.906–2.283	0.123	1.186	0.409–3.439	0.754	1.327	0.425–4.144	0.627
Leukocytes	1.034	0.993–1.077	0.109	0.792	0.635–0.987	0.038	0.747	0.582–0.957	0.021
Neutrophils	1.007	0.990–1.024	0.427	1.144	0.935–1.399	0.192	1.182	0.953–1.467	0.128
Lymphocytes	0.947	0.860–1.044	0.272	0.625	0.201–1.940	0.416	0.492	0.147–1.648	0.250
NLR	1.013	1.000–1.026	0.057	1.003	0.920–1.093	0.946	1.007	0.920–1.103	0.880
LDH*	1.002	1.001–1.003	< 0.001	1.003	1.000–1.006	0.024	5.491	1.657–18.199	0.005
CRP	1.005	1.002–1.008	< 0.001	1.000	0.993–1.008	0.950	1.002	0.993–1.010	0.691
D–dimer	1.054	1.009–1.102	0.020	1.020	0.958–1.082	0.533	1.003	1.000–1.006	0.062
IL–6	1.002	1.000–1.004	0.109	1.002	0.999–1.005	0.217	1.007	0.943–1.074	0.845
Constant				0.002		0.005	0.123		0.125

OR – odds ratio; CI – confidence interval; NLR – neutrophil-to-lymphocyte ratio; LDH – lactate dehydrogenase; CRP – C-reactive protein; IL – interleukin.
***Note*: * multivariate model 2: age > 64 years, LDH > 395 U/L; Hosmer-Lemeshow test *p* = 0.839.**

≥ 2 mg/L and received therapeutic anticoagulation according to the institutional protocol.

First, patients in D-dG with D-dimer levels ≥ 2 mg/L were compared with patients managed using anti-Xa–guided anticoagulation. In the within-group follow-up analysis, CRP and LDH values decreased significantly in both groups (all $p < 0.001$). In the A-XaG group, NLR decreased significantly ($p < 0.001$), whereas in D-dG, NLR increased significantly ($p < 0.001$). D-dimer levels did not change significantly in A-XaG ($p = 0.662$), but increased significantly in D-dG ($p = 0.005$). In the between-group comparison at the final measurement, CRP values remained significantly higher in D-dG than in A-XaG ($p < 0.001$), while D-dimer was also higher in D-dG, with borderline statistical significance ($p = 0.050$). These biomarker dynamics are presented in Supplementary Table 1. Clinical outcomes in this subgroup also differed between strategies. Mortality was higher in D-dG than in A-XaG [120/216 (55.6%) vs. 55/137 (40.1%), $p = 0.007$], and thromboembolic complications were more frequent in D-dG [24/216 (11.1%) vs. 4/137 (2.9%), $p = 0.005$]. These outcomes are summarized in Supplementary Table 1.

Within the overall cohort, 296 (74.9%) patients received therapeutic anticoagulation alone, whereas 57 (14.4%) patients received therapeutic anticoagulation combined with concomitant antiplatelet therapy. An exploratory comparison was performed between these groups. CRP values decreased significantly during follow-up in both groups, whereas LDH decreased significantly only in the therapeutic anticoagulation-alone group. NLR also changed significantly in both groups, although without a decrease over time. No statistically significant differences were observed between groups in mortality ($p = 0.517$) or thromboembolic complications ($p = 0.063$). Detailed results are presented in Supplementary Table 2.

Discussion

In this cohort of critically ill patients with COVID-19, anti-Xa–guided anticoagulation was associated with lower LDH, CRP, and D-dimer levels compared with D-dimer–guided anticoagulation. These findings suggest that individualized anticoagulation monitoring may be associated with

differences in coagulation and inflammatory biomarker trajectories in severe COVID-19. Because the two anticoagulation strategies were implemented sequentially during different phases of the pandemic, temporal changes in clinical management may also have contributed to observed differences between groups. In addition, age, LDH, CRP, and D-dimer were associated with mortality in this cohort, supporting previous evidence linking these markers to disease severity and adverse outcomes [7–10]. Our findings should be interpreted within the context of limited published data examining the relationship between anticoagulation monitoring strategies and inflammatory biomarker dynamics in critically ill COVID-19 patients.

Our previous study provides a detailed comparative analysis of demographic characteristics, comorbidities, pharmacological treatments, mortality rates, and the incidence of thromboembolic and hemorrhagic complications [12].

Anticoagulation therapy has become an important component of the management of hospitalized patients diagnosed with COVID-19 [13]. However, the precise physiological mechanisms underlying this therapy remain to be explored. Anticoagulation therapy may mitigate coagulopathy by partially reducing thrombin generation and may also be associated with modulation of the inflammatory response associated with lung tissue damage in acute respiratory distress syndrome [14, 15]. Given these considerations, anti-Xa–guided anticoagulation may represent a more individualized approach to anticoagulation management in critically ill COVID-19 patients, particularly in those exhibiting a procoagulant state and concurrent hyperinflammation [16].

NLR has emerged as an important prognostic biomarker in COVID-19, with studies showing that higher NLR values at admission are linked to increased disease severity and mortality [17–20]. In our study, non-survivors had higher NLR levels than survivors. Additionally, CRP, LDH, and D-dimer levels were significantly higher in non-survivors, supporting previous studies linking elevated levels of these biomarkers with increased mortality risk [21–24].

In the univariate analysis, significant prognostic factors for mortality were age, LDH, CRP, and D-dimer. In the multivariate analysis, age and LDH showed the most consistent independent associations with mortality. In our cohort, LDH levels above the ROC-derived cut-off value of 395 U/L were associated with an increased risk of mortality. Consistent with this, another study found that elevated LDH levels are associated with approximately a six-fold increase in the risk of severe disease and a sixteen-fold increase in mortality among COVID-19 patients [25]. Furthermore, Li et al. [26] identified a strong association between LDH levels exceeding 445 U/L and severe cases.

Elevated CRP, LDH, and D-dimer levels are associated with increased disease severity in COVID-19 [27–32]. In our study, A-XaG showed lower CRP, LDH, and D-dimer levels over time compared with D-dG. D-dimer levels increased during follow-up in D-dG, whereas a non-significant decrease was observed in A-XaG. In our previous analysis of the same cohort, the D-dimer–guided strategy was associated with higher mortality and a greater incidence of thromboembolic complications than anti-Xa–guided anticoagulation [12]. Taken together, these observations suggest a possible association between protocol-based anticoagulation strategy and longitudinal changes in coagulation and inflammatory biomarkers and clinical outcomes, supporting further investigation in prospective studies.

An additional exploratory subgroup analysis showed findings broadly consistent with the main study results. In the within-group follow-up analysis, CRP and LDH levels decreased significantly in both groups. In contrast, the NLR decreased in A-XaG but increased in D-dG, whereas D-dimer remained unchanged in A-XaG but increased in D-dG. In the between-group comparison at the final measurement, CRP remained significantly higher in D-dG, while D-dimer was also higher with borderline statistical significance. Mortality and thromboembolic complications were also more frequent in D-dG. However, because these analyses were exploratory, they should be interpreted cautiously.

D-dimer reflects plasmin-mediated degradation of cross-linked fibrin and, therefore, indicates prior fibrin formation and activation of the fibrinolytic system [33]. Plasmin is generated from plasminogen *via* tissue-type and urokinase-type plasminogen activators and is rapidly inhibited by α2-antiplasmin [34]. Accordingly, measurable D-dimer levels require prior formation of cross-linked fibrin followed by sufficient plasmin-mediated fibrinolysis despite endogenous inhibitory mechanisms [35]. Although plasmin-antiplasmin complexes may represent a more direct indicator of plasmin generation, D-dimer reflects downstream fibrin turnover and remains the most widely available laboratory marker in routine clinical practice [33, 35]. Fibrinolytic responses in COVID-19 appear heterogeneous, with reports of both enhanced fibrinolysis and relative hypofibrinolysis or fibrinolysis shutdown, potentially related to endothelial dysfunction and dysregulated plasminogen-plasmin pathways [36, 37]. Accordingly, D-dimer should not be interpreted as a direct measure of thrombus burden, but rather as an indirect marker of fibrin formation and turnover [38]. In our study, D-dimer was used as a clinically accessible marker to guide anticoagulation intensity rather than as a diagnostic screening test for thrombosis.

COVID-19–associated coagulopathy also differs from classical consumptive disseminated intravascular coagulation observed in advanced stages of sepsis [36, 39]. Instead, it shares key features with early sepsis-associated coagulopathy, including inflammation-driven thrombin generation, preserved or elevated fibrinogen levels, and a predominantly hypercoagulable phenotype, sometimes accompanied by a relative shutdown of fibrinolysis [39, 40]. Accordingly, D-dimer may be interpreted as a marker of disease severity rather than as a marker of overt consumptive coagulopathy [36, 38, 39].

Our results should be interpreted in the context of current evidence from large randomized platform trials [Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP)/Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 Acute (ACTIV–4a)/Anti-Thrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC)], which showed that routine fixed therapeutic-dose heparin did

not improve outcomes in critically ill patients without confirmed thrombosis, supporting recommendations for prophylactic-intensity anticoagulation in this population [41, 42]. In contrast, the anticoagulation strategy in this study was not based on uniform therapeutic dosing but on individualized titration according to measured anti-Xa activity. In the studied cohort, this protocol-based strategy was associated with lower observed mortality and fewer thromboembolic complications, without an increase in bleeding, compared with the D-dimer–guided protocol [12]. These findings raise the possibility that optimization of the achieved anticoagulant effect, rather than routine fixed therapeutic dosing, may warrant further study in selected high-risk critically ill patients. However, given the observational design of our study, these results should be considered hypothesis-generating and require confirmation in prospective randomized trials specifically evaluating anti-Xa–guided strategies.

Although mean nadroparin dose data were not available for analysis, anticoagulation intensity in our study was interpreted primarily according to protocol allocation and the achieved anticoagulant effect, as reflected by anti-Xa activity, rather than according to the administered dose alone. This approach may be relevant in critically ill COVID-19 patients, in whom interindividual variability in LMWH pharmacokinetics and altered heparin responsiveness have been described [43, 44]. In this context, the administered dose may not fully reflect the actual anticoagulant effect, whereas anti-Xa monitoring may better represent the achieved anticoagulation intensity [45, 46]. At the same time, because anti-Xa–guided dose adjustments were performed in all patients with subtherapeutic anti-Xa levels, some patients in this group may have received higher absolute nadroparin doses than those typically used in standard weight-based therapeutic regimens. Similarly, major randomized COVID-19 anticoagulation trials, including the REMAP-CAP/ACTIV-4a/ATTACC platform and the HEP-COVID trial, primarily compared protocol-based anticoagulation strategies [41, 42, 47]. Nevertheless, in the absence of detailed dose data, the present findings should be interpreted with appropriate caution.

Given the retrospective design and the sequential implementation of treatment protocols, residual confounding related to temporal changes in the standard of care during the pandemic cannot be excluded.

Platelet hyperactivation has also been implicated in the pathophysiology of COVID-19–associated immunothrombosis through interactions with activated endothelium, leukocytes, and neutrophil extracellular traps, potentially contributing to microvascular thrombosis [48–50]. However, the present study was designed to evaluate anticoagulation strategies targeting the enzymatic coagulation cascade rather than platelet inhibition. Antiplatelet therapy was not introduced as part of the study protocol; patients already receiving antiplatelet agents prior to admission continued therapy according to standard clinical practice, and no significant difference in antiplatelet use was observed between groups. Future prospective studies integrating antiplatelet and anticoagulant strategies may further clarify the contribution of platelet hyperactivation and the potential benefit of platelet-targeted therapy in selected patients with immunothrombotic states.

Our results are consistent with the hypothesis that anti-Xa–guided anticoagulation may be associated with a more favorable biomarker profile, potentially related in part to pleiotropic effects of heparins beyond their primary anticoagulant properties [51]. In addition to inhibiting thrombin generation, heparins have been investigated as modulators of inflammatory processes in critically ill patients with sepsis [52]. They may interact with chemokines, cytokines, components of the complement system, activated endothelial cells, and macrophages, potentially attenuating inflammatory signaling [53–55]. Evidence from two meta-analyses has suggested potential benefits of heparins in critically ill patients with sepsis, including reduced 28-day mortality [56, 57].

Nevertheless, heparin-induced thrombocytopenia remains an important clinical consideration during prolonged anticoagulation, even though its risk is lower with LMWH than with unfractionated heparin. Current evidence suggests that heparin-induced thrombocytopenia is generally uncommon in patients with COVID-19; however, because its incidence may be higher among critically ill patients, continued vigilance remains warranted [58].

Anti-Xa–guided monitoring may help refine anticoagulant dose titration in critically ill patients, who are particularly vulnerable to variability in therapeutic response. Reflecting the achieved anticoagulant effect may provide a more direct measure of anticoagulation intensity. Further prospective studies are needed to clarify the role of anti-Xa–guided strategies in optimizing anticoagulation management in critically ill populations.

Limitations of the study

This study has several limitations that should be acknowledged. First, the retrospective, single-center, nonrandomized design may introduce bias and limit generalizability. The two anticoagulation protocols were implemented sequentially during different phases of the pandemic, and, therefore, residual temporal confounding related to evolving standards of care cannot be excluded. Second, the unequal group sizes reflect the sequential implementation of anticoagulation protocols across different phases of the pandemic. Although such an imbalance may reduce statistical precision in the smaller group, diagnostic checks did not indicate major violations of model assumptions. Third, detailed nadroparin dose data were unavailable; therefore, anticoagulation intensity was interpreted based on protocol allocation and the achieved anticoagulant effect (anti-Xa activity), rather than the administered dose alone.

Viscoelastic whole-blood coagulation assays, which may provide a more global assessment of coagulation dynamics and hypercoagulability, were not available in the dedicated COVID-19 unit during the study period, thereby limiting assessment of global hemostatic alterations. Additionally, time-resolved analyses linking the duration of respiratory support to longitudinal changes in coagulation biomarkers were not feasible. Evolving institutional

treatment protocols during the pandemic resulted in differences in the use of immunomodulatory therapy between groups, which may represent a potential source of confounding. Accordingly, residual bias related to differences in immunomodulatory therapy and temporal changes in standard of care cannot be excluded. Because of the retrospective design and the structure of the clinical database, the exact interval between the initial and final laboratory measurements could not be reliably reconstructed for each patient. Laboratory testing was performed according to routine ICU monitoring protocols and was not influenced by anticoagulation group allocation. Furthermore, the number of variables included in the multivariate model was limited to those with established clinical relevance to maintain model stability and interpretability. Finally, prognostic modelling was performed on the overall cohort to assess survival vs. non-survival, and was not powered to evaluate protocol-specific prognostic models within each anticoagulation group. Further prospective studies are warranted to clarify the relationship between anticoagulation therapy and inflammatory biomarkers in critically ill populations.

Conclusion

In this cohort of critically ill patients with COVID-19, anti-Xa–guided anticoagulation was associated with lower levels of lactate dehydrogenase, C-reactive protein, and D-dimer, biomarkers linked to disease severity and progression. These findings suggest that anti-Xa monitoring may represent a more individualized approach to anticoagulation management in critically ill patients; however, given the retrospective design and sequential implementation of treatment protocols, this interpretation should be considered hypothesis-generating. In addition, age and lactate dehydrogenase were independently associated with mortality in multivariate analysis, supporting their prognostic value in this population. Further prospective studies are warranted to clarify the role of individualized anticoagulation strategies in critically ill patients with COVID-19.

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Supplementary Table 1

Inflammatory biomarkers and clinical outcomes among patients receiving therapeutic anticoagulation according to anti-Xa–guided (n = 137) vs. D-dimer–guided (n = 216) strategies

Parameter*	Admission	Final measurement†	*p*-value (within group)
NLR			
A-XaG	12.33 (7.06–21.63)	9.83 (4.20–30.21)	< 0.001[c]
D-dG	11.30 (6.00–21.89)	15.39 (6.06–31.44)	< 0.001[c]
p-value	0.421[b]	0.870[b]	
CRP			
A-XaG	86.30 (40.85–136.65)	16.60 (3.20–55.30)	< 0.001[c]
D-dG	125.00 (60.43–198.80)	38.00 (9.23–138.48)	< 0.001[c]
p-value	< 0.001[b]	< 0.001[b]	
LDH			
A-XaG	422.00 (317.50–623.50)	348.00 (231.00–482.50)	< 0.001[c]
D-dG	483.50 (329.50–662.25)	432.00 (296.00–679.00)	< 0.001[c]
p-value	0.090[b]	0.114[b]	
D-dimer			
A-XaG	1.35 (0.79–3.61)	1.57 (0.72–3.74)	0.662[c]
D-dG	1.64 (0.90–3.76)	2.83 (1.17–6.73)	0.005[c]
p-value	0.241[b]	0.050[b]	
Clinical outcomes	Groups		*p*-value[d]
	A-XaG	D-dG	
Mortality	55 (40.1)	120 (55.6)	0.007
Thromboembolic complications	4 (2.9)	24 (11.1)	0.005[e]

n – number of patients; NLR – neutrophil-to-lymphocyte ratio; A-XaG – anti-Xa group; D-dG – D dimer group; CRP – C-reactive protein; LDH – lactate dehydrogenase.
***Note*: anti-Xa vs. D-dimer group, analysis restricted to patients receiving therapeutic anticoagulation only ([b] Mann-Whitney test); admission vs. final measurement ([c] Wilcoxon test); [d] Chi-squared test; [e] Fisher's test; [*]non-normally distributed data are presented as median (interquartile range); values for clinical outcomes between groups are given as numbers (percentages); [†] final measurement refers to the last recorded value prior to death or discharge.**

Supplementary Table 2

Inflammatory biomarkers and clinical outcomes among patients receiving therapeutic anticoagulation alone vs. therapeutic anticoagulation combined with concomitant antiplatelet therapy

Parameter*	Admission	Final measurement†	*p*-value (within group)
NLR			
TA	12.18 (6.50–21.36)	12.29 (4.91–30.81)	0.002[c]
TA + antiplatelets	11.00 (6.02–21.98)	16.14 (6.38–33.25)	0.035[c]
p-value	0.937[b]	0.112[b]	
CRP			
TA	106.0 (53.98–178.35)	26.45 (6.20–91.02)	< 0.001[c]
TA + antiplatelets	110.80 (40.95–176.15)	46.00 (7.05–163.85)	0.008[c]
p-value	0.790[b]	0.002[b]	
LDH			
TA	468.50 (321.00–656.50)	399.50 (274.25–604.75)	0.005[c]
TA + antiplatelets	436.00 (333.50–619.00)	365.5 (264.25–539.00)	0.105[c]
p-value	0.605[b]	0.852[b]	
D-dimer			
TA	1.56 (0.80–3.55)	2.28 (0.96–4.52)	0.117[c]
TA + antiplatelets	1.53 (0.99–4.97)	2.43 (1.09–6.74)	0.218[c]
p-value	0.583[b]	0.140[b]	
Clinical outcomes	Therapy		*p*-value[d]
	TA (n = 296)	TA + antiplatelets (n = 57)	
Mortality	144 (48.6)	31 (54.4)	0.517
Thromboembolic complications	27 (9.1)	1 (1.8)	0.063[e]

NLR – neutrophil-to-lymphocyte ratio; CRP – C-reactive protein; LDH – lactate dehydrogenase; TA – therapeutic anticoagulation; n – number of patients.
***Note:* TA vs. TA + antiplatelet therapy ([b] Mann-Whitney test); admission vs. final measurement ([c] Wilcoxon test); [d] Chi-squared test; [e] Fisher's test; [*] non-normally distributed data are presented as median (interquartile range); values for clinical outcomes between TA and TA + antiplatelet therapy are given as numbers (percentages); [†] final measurement refers to the last recorded value prior to death or discharge.**