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Anticoagulation therapy in children with SARS-CoV-2 pneumonia: a retrospective observational study on dosage, efficacy, and safety

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Abstract

Background Coagulopathy is a significant complication in pediatric COVID-19, yet optimal anticoagulation dosing in children remains uncertain due to the lack of randomized controlled trials. This study aimed to compare the efficacy and safety of prophylactic versus therapeutic anticoagulation dosing in children hospitalized with SARS-CoV-2 pneumonia.

Methods A retrospective observational study was conducted at Children's Hospital 1 in Ho Chi Minh City, Vietnam, from July 2021 to May 2022. Pediatric patients with confirmed COVID-19 who received enoxaparin were included. Following the national paediatric protocol, patients were stratified by enoxaparin dose into a prophylactic-dose group (0.5 mg/kg every 12 h; total ≤ 1 mg/kg/day) and a therapeutic-dose group (1 mg/kg every 12 h; total > 1 mg/kg/day). Because thrombotic events and deaths were rare, length of hospital stay and changes in inflammatory and coagulation biomarkers were examined as exploratory surrogate outcomes, while in-hospital mortality and bleeding events were reported descriptively. Multivariable regression and inverse probability of treatment weighting (IPTW) were used to reduce, but not eliminate, confounding by indication.

Results Of 181 eligible patients, 140 were included (99 prophylactic-dose, 41 therapeutic-dose). The therapeutic-dose group had a higher proportion of severe/critical disease (82.9% vs. 55.6%, $p = 0.003$). After multivariable adjustment, therapeutic dosing was not associated with a significant difference in length of hospital stay (β = 0.041, 95% CI: −0.165 to 0.246, $p = 0.698$), changes in D-dimer (β = 0.195, $p = 0.797$), C-reactive protein (β = 0.122, $p = 0.985$), or ferritin levels (β = 191.6, $p = 0.509$). No thrombotic events occurred in either group. In-hospital mortality was low (5/140, 3.6%) and did not differ between the prophylactic- and therapeutic-dose groups (4.0% vs. 2.4%, $p = 1.000$). Major bleeding was confined to two patients (4.9%) in the therapeutic-dose group; with only two events, no reliable safety comparison between dosing strategies was possible. IPTW sensitivity analysis was consistent with these results.

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Conclusions After adjusting for disease severity and other confounders, we did not detect a statistically significant difference in efficacy outcomes between prophylactic- and therapeutic-dose anticoagulation. Because of the retrospective design, small sample, strong confounding by indication, and the absence of thrombotic events, these findings are exploratory and hypothesis-generating; the lack of a statistically significant difference should not be interpreted as evidence of equivalence between the two strategies. Prospective, adequately powered studies are needed before any dosing strategy can be recommended for children with SARS-CoV-2 pneumonia, particularly in resource-limited settings where anti-Xa monitoring is unavailable.

Keywords COVID-19, Children, Anticoagulation, Enoxaparin, Prophylactic dose, Therapeutic dose, Efficacy, Safety

Background

Since late 2019, the COVID-19 pandemic has caused a profound global health impact, including in Vietnam, where multiple waves of infection significantly affected the population [1–3]. Although the pandemic has subsided, important questions remain regarding its pathogenesis, optimal treatment strategies, and long-term outcomes [4–6]. One of the most critical clinical concerns has been the coagulopathy associated with severe COVID-19, characterized by a hypercoagulable state that can lead to significant morbidity and mortality [7, 8].

Compared with other respiratory viruses, SARS-CoV-2 infection has been associated with a markedly higher incidence and severity of thrombotic events [9, 10], thought to be driven by inflammatory cascades, immune dysregulation, and vascular endothelial dysfunction [10–12]. In pediatric populations, while thrombotic events are less frequent than in adults, they remain a serious concern that can impact treatment outcomes and lead to long-term sequelae [13, 14]. Accordingly, anticoagulant therapy has been incorporated as a key component of management in severe pediatric COVID-19 cases [15–17].

While adult anticoagulation strategies are guided by robust evidence from large randomized controlled trials (RCTs) and international guidelines [18–21], anticoagulation practices in children remain variable and largely based on extrapolation from adult data [22–24]. The International Society on Thrombosis and Haemostasis (ISTH) recommends low-dose anticoagulation with monitoring of anti-factor Xa (anti-Xa) activity [22]; however, implementing such monitoring protocols is often impractical in resource-limited settings. Uncertainties persist regarding optimal dosing strategies, efficacy, and safety profiles of anticoagulant therapy in children with COVID-19 [24–26].

The present study was conducted to compare the efficacy and safety of prophylactic versus therapeutic anticoagulation in children hospitalized with SARS-CoV-2 pneumonia. Importantly, we employed multivariable regression and propensity score methods to address confounding by indication-a major limitation in observational anticoagulation studies, where sicker patients are more likely to receive higher doses. To our knowledge, this is one of the first studies to explore anticoagulant dosing strategies, adjusted for confounders, in pediatric patients with SARS-CoV-2 pneumonia in a Southeast Asian setting.

Methods

Study design and setting

This was a retrospective observational study conducted at Children's Hospital 1 (CH1), a tertiary pediatric referral center in Ho Chi Minh City, Vietnam. The study period spanned from July 25, 2021, to May 31, 2022, corresponding to Vietnam's fourth wave of the COVID-19 pandemic. The study protocol was approved by the Ethics Committee of CH1 (approval code: CS/N1/21/65). Clinical trial number: not applicable.

Participants

All children diagnosed with COVID-19 and who received anticoagulant therapy during the study period were eligible for inclusion. SARS-CoV-2 infection was confirmed via real-time reverse transcription-polymerase chain reaction (RT-PCR). According to the Ministry of Health of Vietnam's treatment protocol, COVID-19 in children is classified into four categories: mild, moderate, severe, and critical. Patients with SARS-CoV-2–associated pneumonia were considered to have moderate disease, while those requiring respiratory or circulatory support were classified as having severe or critical illness. Anticoagulation was indicated for patients with moderate or greater severity. Patients were excluded if follow-up coagulation testing was not available.

The anticoagulant used was low-molecular-weight heparin (enoxaparin), dosed according to the Ministry of Health of Vietnam paediatric COVID-19 protocol. Prophylactic dosing was defined as enoxaparin 0.5 mg/kg administered subcutaneously every 12 h (total 1 mg/kg/day), and therapeutic dosing as 1 mg/kg every 12 h (total 2 mg/kg/day). For older or heavier children (body weight > 40 kg), a fixed ampoule-based regimen was used in place of strict weight-based calculation-half of a 40 mg enoxaparin ampoule (20 mg) twice daily for prophylaxis and one full ampoule (40 mg) twice daily for therapeutic dosing. Because of this combination of weight-based and fixed dosing, patients could not be cleanly separated by a

per-dose milligram-per-kilogram threshold; we therefore classified patients using the total daily dose, with a cut-off of 1 mg/kg/day distinguishing the prophylactic-dose (≤ 1 mg/kg/day) from the therapeutic-dose (> 1 mg/kg/day) group. Prophylactic dosing was generally administered to patients with moderate disease, whereas therapeutic dosing was reserved for patients who were critically ill or had multiple thrombotic risk factors, including markedly elevated D-dimer levels (> 5 times the upper limit of normal), obesity, presence of a central venous catheter, or requirement for invasive mechanical ventilation. In accordance with the protocol, anticoagulation could be escalated from prophylactic to therapeutic dosing during admission if a patient deteriorated clinically; such patients were classified according to the highest (therapeutic) dose received. This escalation pathway means that the therapeutic-dose group was enriched for patients with worsening disease, an important source of confounding that adjustment cannot fully remove (see Limitations). Anti-factor Xa monitoring was not available at our institution during the study period, so achievement of target anti-Xa levels could not be confirmed.

Medical records were reviewed to extract demographic information, clinical history, comorbidities, clinical manifestations, laboratory investigations, and treatment details. Laboratory tests, including complete blood count, coagulation profile (prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer), and inflammatory markers (C-reactive protein, ferritin), were recorded at two time points: at baseline and 48–72 h after treatment initiation. The anti-inflammatory agent utilized dexamethasone, administered at 0.15 mg/kg/day in all patients.

Outcome definitions

The principal clinical rationale for anticoagulation in COVID-19 is the prevention of thrombosis and reduction of mortality. We therefore prespecified thrombotic events and in-hospital mortality as the primary clinical endpoints; however, because both were rare in this paediatric cohort, they were summarised descriptively rather than modelled. Length of hospital stay and changes in inflammatory markers (CRP, ferritin) and D-dimer were examined as exploratory surrogate measures of efficacy and are not substitutes for hard clinical endpoints. In-hospital death and discharge against medical advice were recorded as distinct outcomes; a composite of the two was additionally analysed but, for the reasons set out in the Discussion, is reported as an exploratory secondary analysis only.

Safety assessment focused on bleeding events, classified according to standard criteria. Major bleeding was defined as: (a) fatal bleeding; (b) life-threatening bleeding causing cardiopulmonary compromise requiring intervention; or (c) serious bleeding, including gastrointestinal hemorrhage, macrohematuria, hemoptysis, or any bleeding event necessitating transfusion and discontinuation of anticoagulation. Minor bleeding included subcutaneous hematomas, epistaxis, gingival bleeding, microhematuria, and hematochezia not requiring drug cessation or additional intervention. Additionally, changes in coagulation parameters indicative of a hypocoagulable state were assessed.

Statistical analysis

Categorical variables were presented as frequencies and percentages. Quantitative variables were presented as median (interquartile range, IQR) given the non-normal distribution of most variables. Between-group comparisons were performed using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Within-group changes before and after treatment were assessed using the Wilcoxon signed-rank test.

To address confounding by indication-an inherent limitation of observational studies in which treatment allocation is influenced by disease severity-we employed multiple analytical approaches. First, multivariable linear regression was used to evaluate the independent association of dosing strategy with continuous outcomes (length of hospital stay [log-transformed], changes in D-dimer, CRP, and ferritin), adjusting for age, sex, disease severity, presence of comorbidities, and baseline biomarker levels. Variance inflation factors (VIFs) were computed to assess multicollinearity among covariates; all VIFs were below 1.5, indicating no problematic collinearity. Second, given the low number of clinical events ($n = 13$), a parsimonious multivariable logistic regression model was employed for poor clinical outcomes-defined as in-hospital death or discharge against medical advice-using only three covariates (dosing strategy, disease severity, and comorbidity status) to maintain an acceptable events-per-variable (EPV) ratio. Third, as a sensitivity analysis, we estimated propensity scores using logistic regression based on age, sex, disease severity, comorbidity status, and baseline CRP, and applied inverse probability of treatment weighting (IPTW) with stabilized weights to estimate the average treatment effect. Additionally, bootstrap resampling (2,000 iterations) was performed to validate the robustness of key regression coefficients against residual non-normality (Additional files 1–7). These regression, weighting, and resampling approaches were used as complementary sensitivity analyses to probe the stability of the findings; we emphasise that they reduce, but cannot eliminate, the bias arising from non-random treatment allocation and the small number of clinical events. All regression results should therefore be regarded as exploratory.

All analyses were performed using R software and Python. A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Study population

During the study period, 181 patients diagnosed with COVID-19 received anticoagulant therapy. Forty-one patients were excluded due to the absence of follow-up coagulation testing, yielding a final cohort of 140 participants: 99 (70.7%) in the prophylactic-dose group and 41 (29.3%) in the therapeutic-dose group.

The median age was 4 years (IQR: 3–10 years), with a male-to-female ratio of 1.6:1. Nearly half of the patients (45.7%) had underlying medical conditions, most commonly obesity (15.7%), neurological disorders (10.0%), and congenital heart disease (5.7%). The therapeutic-dose group was significantly older (median 6 vs. 3 years, $p < 0.05$), had a higher proportion of severe/critical disease (82.9% vs. 55.6%, $p = 0.003$), greater need for respiratory support (90.2% vs. 67.7%), and higher baseline CRP levels (median 11.0 vs. 2.6 mg/L). There were no significant differences in the prevalence of underlying conditions between the two groups. Baseline characteristics are summarized in Table 1.

Clinical efficacy

No thrombotic events, including pulmonary embolism or venous thromboembolism, were observed in either dosing group. In-hospital mortality in the analysed cohort was low (5/140, 3.6%) and did not differ significantly between the prophylactic-dose group (4/99, 4.0%) and the therapeutic-dose group (1/41, 2.4%; Fisher's exact test, $p = 1.000$). One additional death occurred among the 41 patients excluded for absent follow-up coagulation testing, giving six deaths over the full study period. Because thrombotic events did not occur and deaths were few, neither endpoint was suitable for multivariable modelling, and both are reported descriptively. The overall median length of hospital stay was 10.5 days (IQR: 8–14), with no statistically significant difference between the prophylactic-dose group (median 10 days, IQR: 8–13) and the therapeutic-dose group (median 11 days, IQR: 9–14; $p = 0.522$).

Both dosing groups demonstrated statistically significant reductions in CRP levels following treatment (Wilcoxon signed-rank test: prophylactic group, $p < 0.001$; therapeutic group, $p = 0.002$). D-dimer levels showed a trend toward reduction in both groups, though these changes did not reach statistical significance (prophylactic, $p = 0.104$; therapeutic, $p = 0.132$). When comparing the magnitude of change between groups, the therapeutic-dose group showed a greater absolute reduction in CRP (median ΔCRP: −3.84 vs. − 0.20 mg/L, $p = 0.019$);

Table 1 Clinical, laboratory, and treatment characteristics of the study population

Characteristics	Total ($n = 140$)	Prophylactic dose ($n = 99$)	Therapeutic dose ($n = 41$)	*p*-value
Clinical symptoms, *n* (%)				
Fever	116 (82.9)	81 (81.8)	35 (85.4)	0.61[a]
Cough	107 (76.4)	73 (73.7)	34 (82.9)	0.24[a]
Dyspnea/tachypnea	90 (64.3)	57 (57.6)	33 (80.5)	0.01[a]
Vomiting	33 (23.6)	31 (31.3)	2 (4.9)	< 0.001[b]
Diarrhea	31 (22.1)	25 (25.3)	6 (14.6)	0.17[a]
COVID-19 severity, n (%)				
Moderate	51 (36.4)	44 (44.4)	7 (17.1)	0.002[a]
Severe/critical	89 (63.6)	55 (55.6)	34 (82.9)	0.002[a]
Laboratory values, median (IQR)				
WBC count ($\times 10^9$/L)	8.1 (5.7–11.6)	8.7 (5.9–11.7)	6.6 (5.6–11.6)	0.78[c]
Neutrophil count ($\times 10^9$/L)	3.4 (1.9–6.2)	3.1 (1.9–5.5)	4.2 (6.0–6.7)	0.07[c]
Lymphocyte count ($\times 10^9$/L)	2.9 (1.7–5.0)	3.2 (1.8–5.7)	2.1 (3.5–3.7)	0.18[c]
Platelet count ($\times 10^9$/L)	267 (207–355)	280 (205–353)	259 (209–358)	0.94[c]
CRP (mg/L)	3.4 (0.5–25.4)	2.6 (0.4–12.1)	10.9 (0.8–58.1)	0.08[c]
CRP > 20 mg/L, n (%)	37 (26.4)	21 (21.2)	16 (39.0)	0.03[a]
Ferritin (µg/L)	433 (205–669)	367 (188–618)	543 (299–712)	0.31[c]
Elevated ferritin, n (%)	60 (42.7)	37 (37.4)	23 (56.1)	0.04[a]
PT (s)	13.6 (12.4–15.0)	13.7 (12.4–15.1)	12.9 (12.2–14.0)	0.07[c]
aPTT (s)	33.9 (31.0–38.1)	34.4 (31.4–38.5)	32.1 (29.3–35.1)	0.41[c]
Fibrinogen (g/L)	3.0 (2.3–3.9)	2.9 (2.2–3.8)	3.2 (2.5–4.4)	0.15[c]
D-dimer (µg/mL)	0.9 (0.6–1.6)	0.9 (0.6–1.7)	0.8 (0.5–1.4)	0.41[c]
D-dimer > 5×ULN, n (%)	22 (15.7)	15 (15.2)	7 (17.1)	0.78[a]
Treatment, n (%)				
Respiratory support	103 (73.6)	66 (66.7)	37 (90.2)	0.003[b]
Oxygen	63 (45.0)	47 (47.5)	16 (39.0)	0.36[a]
NCPAP	10 (7.1)	8 (8.1)	2 (4.9)	0.72[b]
HFNC/NIV	16 (11.4)	4 (4.0)	12 (29.3)	< 0.001[b]
Invasive ventilation	14 (10.0)	7 (7.1)	7 (17.1)	0.07[a]
Respiratory support, days	4 (0–8)	4 (0–6)	7 (4–10)	0.001[c]
Remdesivir	90 (64.3)	61 (61.2)	29 (70.3)	0.31[a]
Anti-inflammatory	133 (95.0)	93 (93.9)	40 (97.6)	0.67[b]

Table 1 (continued)

Characteristics	Total (*n* = 140)	Prophylactic dose (*n* = 99)	Therapeutic dose (*n* = 41)	*p*-value
Anti-inflammatory, days	9 (7–10)	8 (7–10)	9 (8–10)	0.04[c]
Anticoagulant, days	9 (7–11)	8 (7–10)	10 (8–12)	0.002[c]

IQR interquartile range, *WBC* white blood cells, *CRP* C-reactive protein, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *ULN* upper limit of normal, *NCPAP* nasal continuous positive airway pressure, *HFNC* high-flow nasal cannula, *NIV* noninvasive ventilation

[a] Chi-square test, [b] Fisher's exact test, [c] Mann–Whitney U test

however, this likely reflects the higher baseline CRP in the therapeutic group rather than a true treatment effect. Changes in D-dimer and ferritin did not differ significantly between groups (Table 1; Fig. 1).

Multivariable analysis

Given that the therapeutic-dose group had significantly more severe disease at baseline, multivariable regression was performed to adjust for confounding by indication (Tables 2 and 3).

In the multivariable linear regression model for length of hospital stay (log-transformed), therapeutic dosing was not independently associated with hospital stay duration after adjustment for age, sex, disease severity, comorbidities, and baseline CRP and D-dimer levels (β = 0.041, 95% CI: −0.165 to 0.246, $p = 0.698$). The only significant predictor was disease severity (β = 0.233, 95% CI: 0.044 to 0.422, $p = 0.017$), indicating that severe/critical disease was associated with approximately 26% longer hospital stay independent of dosing strategy (Table 2).

Similarly, multivariable models for changes in biomarker levels showed no significant independent association with dosing strategy. Therapeutic dosing was not associated with greater reductions in D-dimer (β = 0.195, $p = 0.797$), CRP (β = 0.122, $p = 0.985$), or ferritin (β = 191.6, $p = 0.509$) after adjustment for covariates (Table 3). Notably, the model for D-dimer change had a poor overall fit (F-test $p = 0.217$, adjusted $R^2 = 0.019$), and these results should be interpreted with caution. In contrast, the models for CRP and ferritin changes showed adequate fit (F-test $p < 0.001$ for both; Additional file 6). The dominant predictor of biomarker change in each model was the biomarker's baseline level (regression to the mean).

As an exploratory secondary analysis, multivariable logistic regression for a composite poor outcome (in-hospital death or discharge against medical advice; 13 events) was performed using a parsimonious model with three covariates (events-per-variable ratio = 4.3, below the conventional threshold of 10). Therapeutic dosing was not significantly associated with the composite outcome (OR = 1.11, 95% CI: 0.26–4.83, $p = 0.888$), and comorbidity was associated with higher odds (OR = 4.62, 95% CI: 1.24–17.21, $p = 0.023$). Severe/critical disease was associated with apparently lower odds of the composite outcome (OR = 0.15, 95% CI: 0.04–0.57, $p = 0.005$). This counter-intuitive result is an artefact of the composite definition rather than a protective effect: discharge against medical advice accounted for 8 of the 13 events and was concentrated in moderate-severity patients (7/8). When the two components were examined separately, the paradox disappeared for mortality-in-hospital death occurred in 2/51 (3.9%) moderate versus 3/89 (3.4%) severe/critical patients-whereas discharge against medical advice was far more frequent in moderate disease (7/51, 13.7%) than in severe/critical disease (1/89, 1.1%). The composite model is therefore presented for transparency only and should not be interpreted as indicating that severe disease is protective (Table 4; full six-covariate model in Additional file 5; outcome breakdown in Additional file 8).

As a sensitivity analysis, IPTW with stabilized propensity score weights demonstrated adequate overlap between groups (propensity score range: 0.067–0.687). The IPTW weighed mean hospital stay was 12.6 days in the prophylactic group and 15.3 days in the therapeutic group, with no statistically significant difference, consistent with the primary regression results (Additional file 7).

Safety

No fatal or life-threatening bleeding events were observed. Two patients (4.9%) in the therapeutic-dose group experienced upper gastrointestinal bleeding, presenting as hematochezia. Both required red blood cell transfusions and proton pump inhibitor therapy. Bleeding was successfully controlled after discontinuation of anticoagulants and conservative management without endoscopic or surgical intervention. No major bleeding events were observed in the prophylactic-dose group. With only two major bleeding events in the entire cohort, however, the difference in major bleeding between dosing groups could not be assessed statistically, and this descriptive observation should be interpreted with caution.

Minor bleeding events, including subcutaneous hematomas, epistaxis, and gingival bleeding, were more frequent in the therapeutic-dose group, though the difference did not reach statistical significance (Fisher's exact test, $p > 0.05$). Coagulation parameters indicative of a hypocoagulable state (prolonged PT, prolonged aPTT, decreased fibrinogen) showed a trend toward greater derangement in the therapeutic-dose group following treatment (Fig. 2).

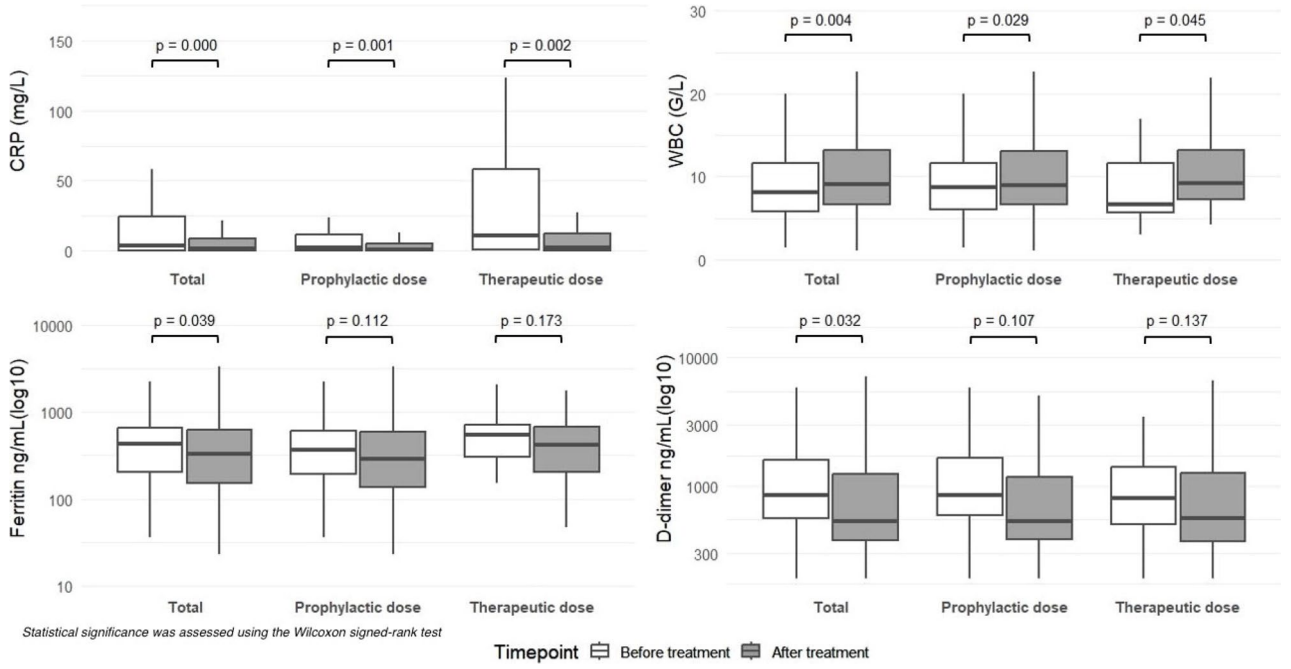


Fig. 1 Changes in inflammatory markers and D-dimer levels before and after treatment in the study population. Box plots showing the distribution of C-reactive protein (CRP), ferritin, and D-dimer levels at baseline and 48–72 hours after treatment initiation in the prophylactic-dose and therapeutic-dose groups. The Wilcoxon signed-rank test was used for within-group comparisons

Table 2 Multivariable linear regression for length of hospital stay (log-transformed), $n = 139$

Variable	β	95% CI	SE	*p*-value
Therapeutic dose (vs. prophylactic)	0.041	−0.165 to 0.246	0.105	0.698
Age (years)	0.009	−0.012 to 0.030	0.011	0.395
Male sex	0.037	−0.141 to 0.214	0.091	0.687
Severe/critical disease	**0.233**	**0.044 to 0.422**	**0.096**	**0.017**
Presence of comorbidity	0.153	−0.035 to 0.341	0.096	0.113
Baseline CRP (log-transformed)	−0.047	−0.108 to 0.014	0.031	0.134
Baseline D-dimer (log-transformed)	0.038	−0.127 to 0.203	0.084	0.651

Overall model: F-test $p = 0.065$, adjusted $R^2 = 0.047$

CI confidence interval, *SE* standard error, *CRP* C-reactive protein

Bold indicates statistical significance ($p < 0.05$)

Table 3 Multivariable linear regression for changes in biomarkers after anticoagulant treatment

Variable	β	95% CI	*p*-value
Change in D-dimer ($n = 139$, Adj. $R^2 = 0.019$)			
Therapeutic dose (vs. prophylactic)	0.195	−1.288 to 1.678	0.797
Severe/critical disease	−0.687	−2.050 to 0.675	0.325
Baseline D-dimer (log)	**−1.427**	**−2.621 to −0.234**	**0.021**
Change in CRP ($n = 134$, Adj. $R^2 = 0.219$)			
Therapeutic dose (vs. prophylactic)	0.122	−12.688 to 12.933	0.985
Severe/critical disease	−9.594	−21.559 to 2.372	0.119
Baseline CRP (log)	**−11.245**	**−15.050 to −7.439**	**< 0.001**
Change in ferritin ($n = 140$, Adj. $R^2 = 0.201$)			
Therapeutic dose (vs. prophylactic)	191.6	−375.0 to 758.2	0.509
Severe/critical disease	166.7	−356.6 to 690.0	0.534
Baseline ferritin (log)	**−645.8**	**−859.0 to −432.6**	**< 0.001**

CI confidence interval,*CRP* C-reactive protein

Bold indicates $p < 0.05$.Models adjusted for age, sex, disease severity, comorbidities, and corresponding baseline biomarker level. The D-dimer model had a poor overall fit (F-test $p = 0.217$, adjusted $R^2 = 0.019$); results for this outcome should be interpreted with caution

Discussion

In this retrospective observational study of 140 children hospitalised with SARS-CoV-2 pneumonia, we did not detect a statistically significant difference in length of hospital stay, biomarker trajectories, or in-hospital mortality between prophylactic- and therapeutic-dose enoxaparin after adjustment for disease severity and other measured confounders. Given the observational design and the strong imbalance in baseline severity between the groups, this absence of a detectable difference must

Table 4 Parsimonious logistic regression for poor clinical outcomes ($n = 140$, events = 13, EPV = 4.3)

Variable	OR	95% CI	*p*-value
Therapeutic dose (vs. prophylactic)	1.11	0.26 to 4.83	0.888
Severe/critical disease	**0.15**	**0.04 to 0.57**	**0.005**
Presence of comorbidity	**4.62**	**1.24 to 17.21**	**0.023**

Poor outcomes are defined as in-hospital death or discharge against medical advice. A parsimonious model with three predictors was used due to the low event count (EPV = 4.3). The paradoxical protective association of severe/critical disease reflects the higher discharge rate against medical advice in the moderate-severity group. Bold indicates $p < 0.05$

OR odds ratio, CI confidence interval, *EPV* events per variable

not be read as evidence that the two strategies are equivalent; the study was neither designed nor powered as a non-inferiority or equivalence trial. The two major bleeding events, both in the therapeutic-dose group, are consistent with the dose-dependent bleeding risk reported in adults, but with so few events no firm conclusion about comparative safety can be drawn.

A methodological strength of the current study is the explicit attempt to address confounding by indication-a critical limitation of observational anticoagulation studies, in which the sickest patients are systematically assigned higher doses. In our cohort, the therapeutic-dose group had significantly more severe disease, higher baseline inflammatory markers, and a greater need for respiratory support, and also included patients escalated from prophylactic dosing because of deterioration. Without adjustment, any comparison of outcomes between dosing groups would be heavily confounded by these baseline differences. After accounting for disease severity, comorbidities, and baseline biomarker levels, therapeutic dosing was not associated with better outcomes for hospital stay, biomarker improvement, or in-hospital mortality, and the IPTW sensitivity analysis was concordant. We stress, however, that these adjustment methods can address only measured confounders; given the small sample and the severity-driven and escalation-driven treatment assignment, meaningful residual confounding is likely to persist, and the analyses cannot demonstrate that the dosing strategies are clinically equivalent.

Our results are consistent with findings from adult cohorts reported in the ACTIV-4a and REMAP-CAP trials [19, 20], which demonstrated that therapeutic-dose anticoagulation did not confer clinical benefit in critically ill patients with COVID-19 and was associated with increased bleeding risk. In non-critically ill patients, therapeutic anticoagulation modestly improved outcomes but was associated with greater bleeding complications [20]. Systematic reviews and observational analyses of anticoagulant intensity in hospitalised and critically ill adults have reached broadly concordant conclusions, with higher-intensity regimens providing limited incremental benefit at the cost of increased bleeding [27–29]. Similarly, a recent prospective meta-analysis by the WHO REACT Working Group found that higher-dose anticoagulation was associated with lower rates of thromboembolic events, but increased bleeding risk, with a net benefit in 28-day mortality observed only in specific subgroups [30].

In the pediatric literature, evidence remains limited. The ISTH consensus recommendations advocate

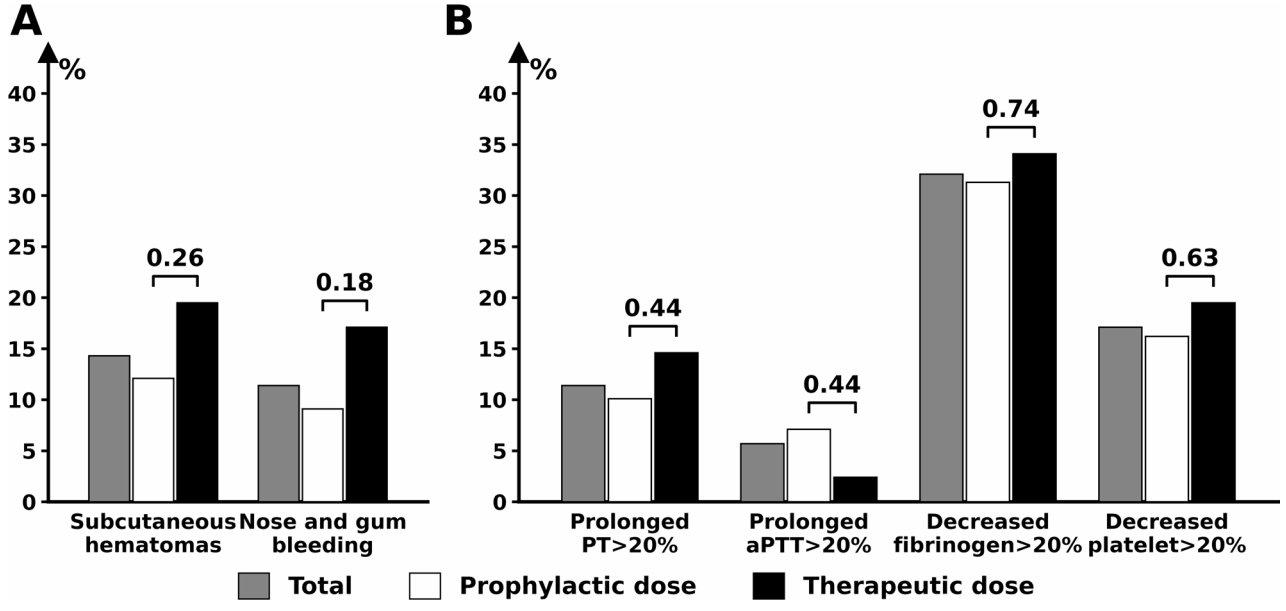


Fig. 2 Characteristics of minor bleeding events and changes in coagulation parameters after treatment. Panel **A**: Distribution of minor bleeding events by type and dosing group. Panel **B**: Changes in prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen levels and platelet count after anticoagulant treatment

for thromboprophylaxis for hospitalized children with COVID-19, with dose escalation based on risk assessment [22]. A systematic review by Xie et al. [23] reported thrombotic event rates of 2.1–4.3% in pediatric COVID-19, with major bleeding rates of 0–3% among those receiving anticoagulation. Our findings are broadly consistent with these data: we observed no thrombotic events (possibly reflecting a lower overall thrombotic burden in children than in adults) and major bleeding in two therapeutic-dose patients. These observations are compatible with, but cannot by themselves establish, a more favourable risk-benefit profile for prophylactic dosing; they should be viewed as hypothesis-generating and interpreted alongside current paediatric guidance rather than as independent support for a particular dosing choice [24].

The finding that baseline biomarker levels were the strongest predictors of biomarker change (rather than dosing strategy) is noteworthy. This regression-to-the-mean phenomenon underscores the importance of accounting for baseline values when interpreting longitudinal changes in biomarkers. Without adjustment, the greater absolute CRP reduction in the therapeutic group could be mistakenly attributed to a superior treatment effect, when in fact it reflects the higher starting values in patients with more severe diseases.

An important methodological consideration in our logistic regression analysis was the paradoxical association between disease severity and the composite poor outcome (OR = 0.15). This finding-whereby severe/critical disease appeared protective-is explained by the composition of the outcome variable. Discharge against medical advice accounted for 8 of the 13 poor outcome events, and 7 of these 8 cases occurred in the moderate-severity group. In the Vietnamese healthcare context, families of moderately ill children are more likely to request early discharge than those of critically ill patients receiving active intensive care support. When the outcome was restricted to in-hospital mortality alone (5 events), the sample was insufficient for meaningful regression modelling. This highlights the importance of carefully defining composite endpoints in pediatric studies conducted in settings where discharge against medical advice is common, as including such events may introduce unexpected associations with severity (Additional file 8).

Our study is particularly relevant to resource-limited settings where anti-Xa monitoring-recommended by the ISTH for guiding enoxaparin dosing-is not routinely available, and where clinicians must rely on weight-based dosing without pharmacodynamic confirmation. Within these constraints, our data are compatible with the hypothesis that prophylactic dosing may provide adequate coverage with an acceptable safety profile, but they do not constitute sufficient evidence to recommend it as a first-line approach. This question should be addressed prospectively before practice recommendations are made.

Several limitations warrant consideration. First, this was a single-centre study with a relatively small sample size, limiting statistical power, particularly for rare outcomes such as mortality and thrombotic events. However, given the lower incidence of severe COVID-19 in children compared with adults, the sample size is reasonably representative. Second, the low number of poor-outcome events ($n = 13$) necessitated a parsimonious logistic regression model with only three covariates (EPV = 4.3), which remains below the recommended threshold of 10 EPV; consequently, results from this model should be interpreted as exploratory. Third, the retrospective design and non-random treatment allocation introduce potential for residual confounding despite our multivariable adjustments. We addressed this using multiple analytical approaches (multivariable regression, IPTW, and bootstrap resampling), yielding consistent results that strengthen the validity of our conclusions (Additional files 2–4). Fourth, residual non-normality was observed in all linear regression models, driven by extreme values (e.g., hospital stay up to 170 days); however, bootstrap sensitivity analyses with 2,000 resamples yielded confidence intervals consistent with parametric estimates (Additional file 2), and heteroscedasticity-consistent standard errors confirmed the primary findings (Additional file 3), supporting the robustness of these findings. Fifth, certain outcomes, such as asymptomatic thrombosis or minor bleeding, may have been underestimated due to the lack of systematic screening at the time. Sixth, the inclusion of discharge against medical advice in the composite poor outcome variable introduced a paradoxical association with disease severity, as discussed above; for this reason the composite was demoted to an exploratory analysis and the components were examined separately. Seventh, and most importantly for interpretation, the principal clinical justification for anticoagulation—prevention of thrombosis and reduction of mortality—could not be directly evaluated, because no thrombotic events occurred and deaths were few. Our efficacy assessment therefore rests on length of stay and biomarker trajectories, which are surrogate measures influenced by many factors other than anticoagulation and are not substitutes for hard clinical endpoints. Finally, as this study was conducted during a single pandemic wave in one centre, its generalizability to other settings, populations, and future viral pneumonias should be considered cautiously.

Conclusions

In this retrospective observational study of children with SARS-CoV-2 pneumonia, we did not detect a statistically significant difference between prophylactic- and

therapeutic-dose enoxaparin in length of stay, biomarker trajectories, or in-hospital mortality after adjustment for disease severity and other measured confounders. No thrombotic events occurred, and the two observed major bleeding events were too few to support a comparative safety conclusion. Because of the retrospective design, small sample, pronounced confounding by indication, and the rarity of the most clinically important endpoints, these findings are exploratory and hypothesis-generating; the absence of a detectable difference should not be interpreted as evidence of equivalence, and our results do not establish prophylactic dosing as a preferred strategy. Adequately powered, prospective multicentre studies-ideally randomised and incorporating clinically meaningful thrombotic and mortality endpoints-are needed before evidence-based anticoagulation recommendations can be made for children with viral pneumonia, particularly in settings where anti-Xa monitoring is unavailable.

Abbreviations

aPTT	Activated partial thromboplastin time
CI	Confidence interval
CRP	C-reactive protein
EPV	Events per variable
HFNC	High-flow nasal cannula
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
ISTH	International Society on Thrombosis and Haemostasis
LMWH	Low-molecular-weight heparin
NCPAP	Nasal continuous positive airway pressure
NIV	Noninvasive ventilation
OR	Odds ratio
PT	Prothrombin time
RCT	Randomized controlled trial
RT-PCR	Real-time reverse transcription-polymerase chain reaction
SE	Standard error
ULN	Upper limit of normal
VIF	Variance inflation factor
WBC	White blood cells

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-026-07392-3.

Additional file 1: Table S1. Variance inflation factors (VIF) for all multivariable regression models. Additional file 2: Table S2. Bootstrap validation of key regression coefficients (2,000 iterations). Additional file 3: Table S3. Heteroscedasticity-consistent (HC3) robust standard errors for linear regression models. Additional file 4: Table S4. Sensitivity analyses for multivariable regression models. Additional file 5: Table S5. Full six-covariate logistic regression model for poor clinical outcomes. Additional file 6: Table S6. Residual diagnostics for linear regression models. Additional file 7: Table S7. Inverse probability of treatment weighting (IPTW) propensity score analysis details. Additional file 8: Table S8. Breakdown of poor clinical outcomes by dosing group and disease severity.

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Authors' contributions
NTNP and MATN conceived and designed the study. TTT and NVN collected the data. DHN and MATN performed the data analysis. NTNP and MATN wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the final manuscript.

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Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Children's Hospital 1, Ho Chi Minh City, Vietnam (approval code: CS/N1/21/65). Informed consent was waived due to the study's retrospective design, in accordance with the Ethics Committee's policies.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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