Targeted interventions in mechanically ventilated patients

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Elevated Unfractionated Heparin Requirement in COVID-19 patients:

exploring influencing factors

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ABSTRACT

Objectives

It has been reported that in patients with COVID-19 associated pulmonary embolism high doses of unfractionated heparin (UFH) are required to achieve activated partial thromboplastin time (APTT) levels within the therapeutic range. The aim of this study was to compare the UFH dose in ICU patients with COVID-19 and control ICU patients and to explore possible explanatory factors.

Design

Retrospective cohort study

Setting

ICU in Leiden University Medical Center in the Netherlands

Patients

COVID-19 patients admitted to the ICU between March 15 2020 and January 1st 2022, and control patients admitted to the ICU between January 1st 2014 and January 1st 2020

Intervention

All patients had an indication for therapeutic UFH. Primary endpoint was the UFH dose given. A mixed linear model was used to assess the relationship between APTT and UFH dose, antithrombin (AT), CRP and BMI.

Measurements and main results

COVID-19 patients received a median UFH dose of 383 (IQR, 303-461) international units (IU) per kilogram per day (IU/kg/day) compared to 308 IU/kg/day (IQR, 253-387 in controls ($p<0.001$). Median APTT was 63 sec (IQR, 53-68) for COVID-19 patients and 66 sec (IQR, 60-70) for controls ($p<0.001$). Overall, median CRP was lower (67 mg/l, IQR 18-145 vs 103 mg/l, IQR 56-180) and median AT values were higher (92%, IQR 78-104 vs 71% IQR, 62-84) in COVID-19 patients. In the mixed linear model, only UFH dose showed a significant relationship with APTT ($p=0.0316$).

Conclusion

COVID-19 patients were administered higher UFH doses but had lower APTT values compared to controls. Lower APTT values could not be explained by either BMI, CRP, or AT levels. Other patient-related factors may account for the difference in heparin administration.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has seriously impacted global public health, leading to more than 750 million infections and almost 7 million deaths (1). Severe cases often involve pulmonary inflammation, necessitating mechanical ventilation and extended intensive care unit (ICU) stay. Patients with COVID-19 may exhibit a prothrombotic state, with venous and arterial thrombotic complications despite receiving adequate thromboprophylaxis (2, 3).

The coagulation activation in COVID-19 differs from the disseminated intravascular coagulation (DIC) seen in sepsis. COVID-19 patient generally have high D-dimer levels but, contrary to patients with DIC, normal platelet and coagulation tests, with CT scans showing pulmonary embolism (PE) mainly in peripheral lung segments, indicating a unique coagulation mechanism (3, 4). Critically ill patients with COVID-related PE are often treated with unfractionated heparin (5). It has been reported that high doses of unfractionated heparin (UFH), often higher than 35000 IU per day, are required to achieve activated partial thromboplastin time (APTT) levels within the therapeutic range (6).

It has been shown that APTT can be impacted by a wide range of preanalytic, analytic or biological factors (7). For instance, during UFH administration elevated levels of FVIII and fibrinogen, along with decreased antithrombin (AT) can shorten APTT levels, while increased CRP, lupus anticoagulants or decreased levels of clotting factors secondary to liver disease can all prolong APTT (7-11). Anti-Xa activity is less affected by the previous mentioned factors, but high antiphospholipid antibody titers can increase measured anti-Xa activity (8). High FVIII, fibrinogen, CRP, and antiphospholipid antibodies as well as low AT hallmarks of COVID-19 coagulopathy, potentially influence UFH dosing (12-14).

The aim of our study was to compare the administered doses of UFH in patients with COVID-19 related PE with a historical cohort of ICU patients treated with UFH for venous thromboembolic disease not related to COVID-19. Furthermore, factors that could explain these differences were explored.

MATERIAL AND METHODS

This retrospective observational cohort study was conducted at ICU of the Leiden University Medical Center (LUMC) in the Netherlands and included two cohorts of patients. The first cohort consisted of all consecutive patients who were admitted to the ICU between March 15, 2020 and January 1st, 2022 for COVID-19 respiratory

failure and treated with UFH for pulmonary embolism. The second cohort included patients admitted to the same ICU between January 1st 2014 and January 1st 2020 who were treated with UFH for venous thromboembolic disease not related to COVID-19. This study was approved by the Institutional Review Board of the LUMC for COVID-19 studies on March 24th 2022, and was registered on clinicaltrials.gov under number NCT05509647. The requirement for informed consent was waived by the medical ethics committee (reference number: CoCo 2022-020, approval date: 24-09-2022) and the study was conducted in accordance with the Declaration of Helsinki.

Patients

Inclusion criteria for the COVID-19 group were as follows: a confirmed COVID-19 diagnosis proven by PCR of nose- or airway sample, admitted to the ICU between March 15, 2020, and January 1st, 2022, aged 18 years or older, and receiving UFH treatment targeting an APTT range of 60-80 seconds and anti-Xa level of 0.3-0.5 IU/ml. For the control group, inclusion criteria were: admitted to the ICU between January 1st 2014 and January 1st 2020, aged 18 years or older, and receiving UFH treatment for any indication targeting an APTT range of 60-80 seconds. Patients who were treated with anticoagulants other than UFH or fibrinolytic agents were excluded from both groups.

Measurements

Data was collected for the entire period patients received UFH therapy. General information on ICU length of stay, hospital length of stay, ICU mortality, hospital mortality, admission type, acute diagnosis, chronic diagnosis, and the use of vasoactive drugs were extracted from the Dutch National Intensive Care Evaluation (NICE) registry database (15). Data on sex, age, BMI, ICU admission and discharge date, anti-Xa (when available), and APTT every 8 hours with corresponding UFH dose were extracted from the electronical medical patient record. Additionally, both CRP and AT levels were measured routinely in COVID-19 patients, but only measured if indicated in control patients. The APTT assays were performed using STA Cephascreen reagent on the STA-R (Evolution) analyser from 2014 to 2017, and the STA-R Max analyser from 2017 to present (STA series: Diagnostica Stago, Asnières-sur-Seine, France). The anti-Xa assays were performed using Chromogenix anti-Xa reagent (Werfen, Barcelona, Spain) on the the STA-R (Evolution) analyser from 2014 to 2017, and from 2017 to 2022 using STA Liquid anti-Xa reagent on the STA-R Max analyser (STA series: Diagnostica Stago, Asnières-sur-Seine, France). Antithrombin activity was analyzed using Chromogenix Coamatic Antithrombin reagent (Werfen, Barcelona, Spain) on the STA-R Evolution analyser from 2014 to 2017, and from 2017 to 2022 using STAChrom AT III reagent on the STA-R Max analyser (STA series: Diagnostica Stago, Asnières-sur-Seine, France). CRP was analyzed using Tinaquant C-Reactive Protein reagent on a Roche Modular

from 2014 to 2017 and from 2017 onwards on a Roche Cobas 8000 analyzer (Roche Diagnostics, Rotkreuz, Switzerland).

Treatment procedures

Patients with confirmed thrombosis or embolism were all treated with intravenous UFH during the complete study period. The detailed UFH dosing protocol can be found in appendix 1. Patients received a loading dose of 70 IU/Kg (max 5000 IU) and a starting dose of 300 IU/kg/24 hours (max 30.000 IU/24 hours). The target APTT was established at 60-80 seconds and APTT was checked every 8 hours. When APTT measurements fell outside the target range, doses were adjusted based on the provided dosing schedule and pump setting adjustments that can be found in appendix 1. Because of apparent difficulties in reaching the target APTT range in COVID-19 patients additional monitoring of anti-Xa levels in addition to APTT, was standard procedure in the cohort of COVID-19 patients, but not in controls. Details on the influence of anti-Xa values on dosing of UFH in COVID-19 patients can be found in appendix 2.

Statistical analysis

All statistical analysis were performed using R language and environment (R Foundation for Statistical Computing, Vienna, Austria, version 4.0.3). Descriptive statistics were used to summarize patient demographics, with comparisons made using unpaired t-tests or Mann-Whitney U tests for continuous variables and Chi-square test for categorical variables.

Our primary endpoint, median UFH dose, was presented as median with interquartile range (IQR). For secondary endpoints, continuous variables were reported as median with IQR. Differences between groups were assessed using a Mann-Whitney U test. The concordance between APTT and anti-Xa was presented using a cross-tabulation with absolute numbers and percentages. Given that APTT values outside the range of 60-80 seconds may reflect the initial titration phase of treatment, we also performed a subgroup analysis focused on cases with APTT levels within the 60-80 range. The lme4 package (Bates, Maechler and Bolker, 2012) in R studio was used to perform a linear mixed effects analysis of the relationship between APTT and various clinical factors. As fixed effects we entered UFH dose, CRP, BMI and AT and as random effects we added intercepts for individual subjects in order to adjust for inter-patient correlation due to repeated measurements. The Restricted Maximum Likelihood (REML) method was employed for model fitting, and the distribution of scaled residuals was examined to validate model assumptions. R2 was calculated to evaluate the predictive value of the model using the performance package (Lüdecke, Ben-Shachar, Patil, Waggoner and Makowski, 2021) in R studio. The linear mixed model was based solely on APTT values ranging from 60 to 80, as values outside this range were considered less

reliable because extreme APTT values, either low or high, are frequently encountered during the adjustment phase of treatment and including these values could potentially compromise the reliability of the model.

Table 1. Patient characteristics. Abbreviations: UFH, Unfractionated Heparin; SAPS, Simplified Acute Physiology Score; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association.

Variables	COVID-19 patients (N=162)	Control patients (N=1006)	P-value
Age (mean (SD))	64 (10)	62 (14)	0.022
BMI (mean (SD))	29 (4)	27 (6)	<0.001
Sex = Female (%)	33 (20)	342 (34)	0.001
ICU length of stay (days) (median (IQR))	15 (10, 29)	8 (3, 19)	<0.001
Hospital length of stay (days) (median (IQR))*	21 (13, 34)	23 (10, 44)	0.619
Duration of UFH therapy (days) (median (IQR))	9 (5, 18)	5 (2, 11)	<0.001
ICU mortality (%)*	58 (36)	254 (25)	0.011
Hospital mortality (%)*	62 (38)	320 (32)	0.183
SAPS II score (median (IQR))*	45 (35, 59)	43 (33, 55)	0.049
Type of admission*, No. (%)			<0.001
Medical	160 (99)	559 (57)	
Emergency surgery	1 (1)	141 (14)	
Elective surgery	1 (1)	282 (29)	
Acute diagnosis*‡, No. (%)			<0.001
Cardiac (including cardiac surgery)	3 (2)	496 (51)	
Sepsis	0 (0)	53 (5)	
Gastrointestinal	0 (0)	94 (10)	
Pneumonia	157 (97)	77 (8)	
Respiratory (other)	2 (2)	124 (12)	
Neurologic	0 (0)	24 (2)	
Trauma	0 (0)	10 (1)	
Transplant	0 (0)	52 (5)	
Other	0 (0)	52 (5)	
Chronic diagnosis*§, No. (%)			
Chronic kidney failure	7 (4)	138 (14)	0.001
Chronic dialysis	0 (0)	32 (3)	0.038
Metastasized neoplasm	2 (1)	25 (3)	0.460
COPD (drug dependent)	8 (5)	68 (7)	0.441
Chronic respiratory insufficiency	6 (4)	27 (3)	0.675
Cardiovascular insufficiency (NYHA IV)	2 (1)	79 (8)	0.003
Liver cirrhosis	1 (1)	43 (4)	0.037
Diabetes	32 (20)	210 (21)	0.713
Haematological malignancy	0 (0)	24 (2)	0.086
Immunological insufficiency	1 (1)	52 (5)	0.015
Vasoactive drugs at ICU admission	128 (79)	779 (79)	1

*Data was missing for 24 patients in the Control group.
‡ Acute diagnosis is classified according to the APACHE IV model
§ More than one chronic diagnosis can be present in the same patient

RESULTS

All 162 consecutive COVID-19 patients and 1006 control patients were included in this study. Patient characteristics are shown in Table 1. Hospital length of stay and hospital mortality were comparable between groups, yet COVID-19 patients were older with a higher BMI and Simplified Acute Physiology Score (SAPS), were more often male, had longer ICU stays, and higher ICU mortality. Furthermore, COVID-19 patients were administered UFH for a median of 9 days (IQR, 5-18), while control patients received UFH for a median duration of 5 days (IQR, 2-11) (p<0.001).

Measurements

The analysis included 7372 APTT measurements in 162 COVID-19 patients and 30946 measurements in 1006 control patients. Median APTT values were 63 sec (IQR, 53-68) for COVID-19 patients and 66 sec (IQR, 60-70) for controls (p<0.001). Median anti-Xa for COVID-19 patients was 0.5 U/ml (IQR 0.4-0.6) (not available in controls). Median UFH dose was 383 (IQR, 303-461) international units (IU) per kilogram per day (IU/kg/day)) in the COVID-19 group and 308 IU/kg/day (IQR, 253-387) in controls (p<0.001). Median CRP was 67 mg/l (IQR, 18-145) for COVID-19 and 103 mg/l (56-180) for controls (p<0.001), and median AT levels were 92% (78-104) for COVID-19 (N=118) and 71% (62-84) for controls (N=18) (p<0.001).

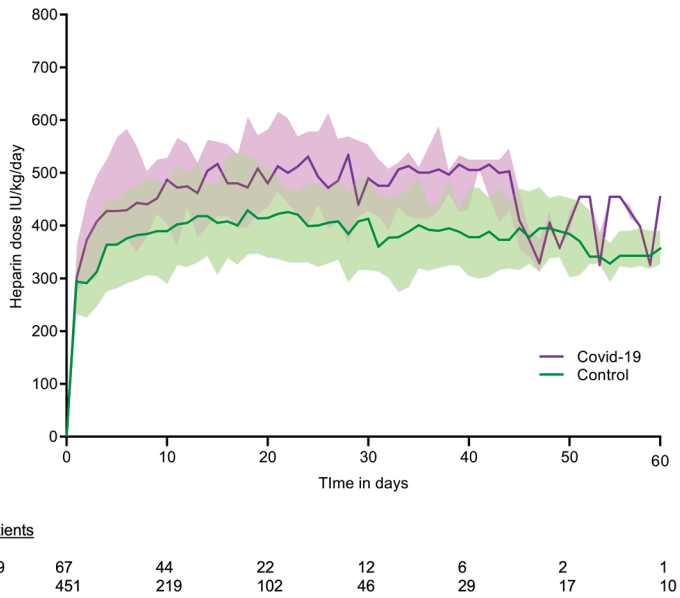

Figure 1. Heparin administration over time. Values represent the median of median values per day per patient. Heparin dosages were only included when APTT was within therapeutic range (60-80 sec).

Measurements within therapeutic range of APTT 60-80

A subgroup analysis only including episodes with APTT 60-80 sec included 3154 measurements in 151 COVID-19 patients and 18450 measurements in 868 control patients. Median APTT values were 68 sec (IQR, 66 – 70) in both the COVID-19 and control group (p=0.5), with a median anti-Xa of 0.6 U/ml (IQR, 0.4-0.9) in the COVID-19 group (not available in controls). The corresponding median UFH dose was 399 IU/kg/day (IQR 330-490) and 330 IU/kg/day (IQR, 267-419) in COVID-19 and control patients (p<0.001, fig 1). Median CRP was lower in COVID-19 patients at 82 mg/l (IQR, 29-150), compared to 103 mg/l (IQR 60-180) in controls (p<0.001). Median AT values were 89% (IQR, 18-145) for COVID-19 (N=97) and 67% (IQR, 56-180) for controls (N=12) (p<0.001).

APTT vs anti-Xa

The distribution of APTT and anti-Xa levels in COVID-19 patients is shown in Figure 2. In table 2, the concordance of APTT and anti-Xa is shown. Concordant APTT and anti-Xa values were observed in 31% of the cases, namely when both APTT and anti-Xa were low (556/4167), both in target (525/4167) or both high (190/4167). In 1471 episodes, APTT was within the therapeutic target-range. In 190 of these cases (13%), anti-Xa was less than 0.3 U/ml, fulfilling the criteria of the local protocol to increase the dose of UFH, and in 756 (51%) anti-Xa was above 0.5 IU/ml, fulfilling the criteria to decrease the dose.

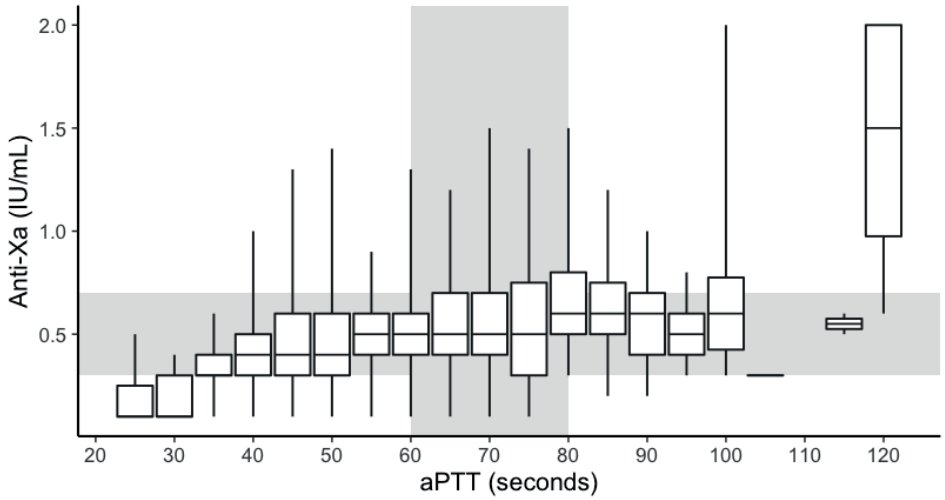

Figure 2. Distribution of APTT and anti-Xa levels in patients with COVID-19. The faded areas represent the ranges for APTT and anti-Xa that were considered 'therapeutic anticoagulation' at the study site (60-80 seconds for APTT, and 0.3-0.5 IU/mL for anti-Xa).

Table 2. Relationship between anti-Xa and APTT values in COVID-19 patients. The gray field indicates that both APTT and anti-Xa measurements were concordant, either falling below, within or above the respective target values.

Categories	Total	anti-Xa <0.3 IU/mL	anti-Xa 0.3-0.5 IU/mL	anti-Xa > 0.5 IU/mL
APTT <60	2392 (100%)	556 (23%)	1066 (45%)	770 (32%)
APTT 60-80	1471 (100%)	190 (13%)	525 (36%)	756 (51%)
APTT >80	304 (100%)	23 (8%)	91 (30%)	190 (63%)
Total	4167	769	2785	613

Association APTT and various clinical factors

A linear mixed model was applied to describe the association between APTT and UFH, CRP, BMI and AT, adjusting for individual differences (cluster effect). The full output of the model can be found in appendix 3. UFH demonstrated an association with APTT (p=0.02). Other potential predictors, including CRP (p=0.1), BMI (p=0.9), and antithrombin (p=0.3) were not associated with APTT. Individual differences, that could not be explained by CRP, AT, BMI, accounted for a substantial proportion of the variability in the model (Variance = 2.429, SD = 1.559). Conditional R2 (0.111) and Marginal R2 (0.030) were both low, indicating that a relevant proportion of the variability in APTT is not explained by the model. The differences between the observed APTT and the predicted APTT for COVID-19 patients can be observed in figure 3.

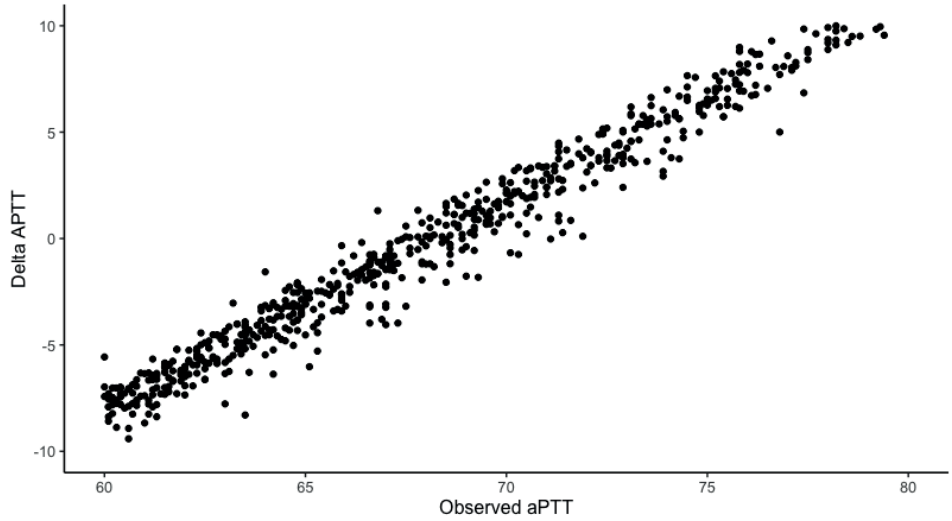

Figure 3. Observed APTT versus the delta APTT in a selection of measurements with APTT between 60 and 80 sec. Delta APTT was calculated as the observed APTT minus the predicted APTT. The mean delta APTT was -0.7 sec with a standard deviation (SD) of 5.4 sec. The model to predict APTT was developed in patients/measurements with APTT between 60 and 80 sec.

DISCUSSION

In this retrospective observational study we show that substantially higher UFH doses were administered to ICU patients with COVID-19 associated pulmonary embolism compared to ICU patients treated with heparin for other indications. This is in accordance with earlier studies reporting that COVID-19 patients may require heparin doses above the conventional therapeutic amounts, often fulfilling the criteria for heparin resistance, in these studies defined as an UFH dose exceeding 35.000 IU/24 hours while APTT is in the therapeutic range (6, 14, 16).

There are several potential explanations for the higher heparin requirements in patients with COVID-19. First, it could be that physicians target at a higher level of anticoagulation in COVID-19 patients. In our cohort, this appears an unlikely explanation. Both COVID-19 and control patients were treated using the same protocolized target range for APTT. In fact, APTT levels were slightly lower in COVID-19 patients compared to non-COVID ICU patients. Furthermore, when selecting only patients within the therapeutic APTT range, the difference in dosing of UFH between COVID and non-COVID patients was even more marked. Another potential explanation is the difference in protocol for dosing of heparin in COVID-19 patients. In contrast to the control population, not only APTT but also anti-Xa levels were measured. Thus, not only low APTT levels, but also low anti-Xa levels could have led to higher heparin doses. However, it is unlikely that additional monitoring of anti-Xa has led to higher heparin doses in our patients. In patients within the therapeutic APTT range, it was much more common that anti-Xa was higher than that it was lower than the target range of 0.3-0.5 IU/ml. Third, higher doses of heparin could also be explained if body mass was higher in patients with COVID-19. Indeed, body mass index was higher in patients with COVID-19, but the difference was limited. Also, in our mixed linear model on factors associated with APTT, BMI was not a relevant predictor. Thus, we conclude that it is highly unlikely that differences in body weight explain our findings.

From the literature, it is well known that higher plasma levels of CRP (6, 14, 16) prolong APTT depending on the type of reagent used. In addition, low AT levels may give rise to heparin resistance and consequently shorter APTT during heparin therapy. Thus, if CRP and /or AT plasma levels were lower in COVID-19 patients, that could be an explanation for relatively short APTT values and consequently lead to higher administered doses of heparin. In our patients with COVID-19 CRP was indeed lower, but AT levels were higher than in control patients. In our mixed linear model, neither CRP nor AT predicted APTT. Thus, there are several reasons why AT and CRP should not be considered as important factors influencing heparin dosing in COVID-19 patients.
As indicated by the low R2 our mixed linear model to describe the association between

APTT and heparin, CRP, AT, and BMI could only explain a small part of the variability of APTT values. Clearly, some other factors must have important influence. We can only speculate what these factors could be. It is known that COVID-19 patients may have a markedly hypercoagulable state, possibly explained by the acute phase response with high factor VIII and fibrinogen levels (9, 11, 17). Indeed, from the literature, we know that factor VIII may be very high in COVID-19 patients (18-20). Unfortunately, in our cohorts, factor VIII and fibrinogen levels were not measured.

In this study, heparin therapy in ICU patients was monitored primarily based on APTT values. In COVID-19 patients, anti-Xa may be more reliable than APTT to monitor UFH therapy (21). In our cohort, when APTT was in the therapeutic range, anti-Xa was higher than 0.5 IU/ml in 51% of measurements. Thus, it appears that monitoring based on APTT may lead to higher doses of UFH than dosing based on anti-Xa. It is possible that higher doses of heparin may lead to an increased risk of bleeding complications (22). A randomized controlled study comparing monitoring UFH with APTT versus anti-Xa in patients with venous thrombosis showed that monitoring based on anti-Xa led to lower doses of administered UFH but without a difference in efficacy or in bleeding complications (23). Unfortunately, in our study data on bleeding complications are not available.

Some limitations of this study should be discussed. Firstly, there were some baseline differences between the two groups. We did not have information on the specific indications for UFH use in individual patients. Whereas pulmonary embolism was the indication for UFH in all COVID-19 patients, in control patients different indications may have been present. Due to the retrospective design, some data, such as information on factor VIII and fibrinogen were not available. Also, different analyzers and methods were used to perform APTT, anti-Xa and antithrombin assays before and after 2017 which may have influenced those measurements in the non-COVID-patients. Since the same APTT reagents were used in both periods, the effect of a different analyzer on the APTT measurement is likely to be minimal. In our data, the median APTT values and UFH dose before and after 2017 were the same. Lastly, not all our findings may be generalizable for other ICUs due to specific local treatment protocols. It is unknown if differences in dosing between COVID-19 and non-COVID patients would still exist if only anti-Xa was used for monitoring of heparin effects. Also, our findings apply for patients treated with UFH, not with LMWH, and AT levels were not available in the majority of the patients.

In conclusion, our data shows a higher UFH dose in COVID-19 patients compared to a historical cohort of ICU patients. Despite a higher UFH dose, APTT values were lower in COVID-19 patients. The lower APTT values could not be explained by either CRP,

BMI, AT, or the additional use of anti-Xa in addition to APTT monitoring. Likely, some other factors may account for this difference in heparin administration. Based on the literature, we hypothesize that higher factor VIII or fibrinogen levels in COVID-19 patients may play a role but this should be investigated in future research.

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