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Original Article

A comparison of anti-coagulation monitoring tests in ICU patients receiving a continuous infusion of unfractionated heparin

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1. Introduction

In the intensive care unit (ICU), continuous intravenous infusion of unfractionated heparin (UFH) is a relatively common form of anticoagulation therapy.[1,2] Monitoring the anticoagulation state during UFH infusion is necessary because of the unpredictable pharmacokinetics of UFH and high inter-individual variability in anticoagulant response. This may lead to under/overdosing.[3,4]

Thus, the optimal approach to monitoring UFH therapy is unknown, and guidelines regarding the preferred laboratory test are not definitive.[5,6] In the ICU, UFH infusion has been typically monitored using activated partial thromboplastin time (aPTT).[7,8] Recently, however, anti-factor Xa (anti-Xa) has been recommended as a more reliable method, though it is expensive and not widely available.[9,10] Conversely, activated clotting time (ACT) has been commonly used for monitoring patients undergoing cardiac surgery and those on ECMO.[11]

These tests may not capture the in vivo complexity and performance of the coagulation system in ICU.

The complexity of anticoagulation monitoring in the ICU is due to two factors: the inherent differences in the tests (valid in any context), and the additional complexity arising from the coagulation state of critically ill patients. As far as the former aspect is concerned, each test examines different aspects of the coagulation process (Fig. 1). Consequently, different conditions will affect aPTT, anti-Xa or ACT in different directions and independently of the effect of UFH, making their values less reliable.

The additional complexity present in ICU patients is also important.[12,13] ICU patients may have both a coagulopathic or a prothrombotic profile, which may even coexist.[14,15] Critically ill patients frequently experience anemia,[16,17] thrombocytopenia[18,19] and/or hypocalcemia,[20–22] all factors that interfere with the performance of the tests and in-vivo coagulation. Moreover, critically ill patients may be receiving other drugs that interfere with anticoagulation (e.g. antiplatelet agents)[23] and may have specific conditions that alter the production of coagulation factors (e.g. liver disease).[24,25] Equally important can be the influence of acute-phase protein release,[26] such as the increase in fibrinogen or factor VIII,[27–29] or the presence of a subclinical consumptive coagulopathy.[30] Moreover, acquired antithrombin deficiency in critically ill patients can lead to an altered response to UFH.[31,32]

Accordingly, we simultaneously measured aPTT, anti-Xa and ACT in ICU patients receiving a UFH infusion. We aimed to test the primary hypothesis that the correlation between these tests would be limited. Moreover, we aimed to test the secondary hypothesis that they would also have limited concordance for pre-defined therapeutic ranges for these tests. Finally, we aimed to explore whether additional haematological variables might show an independent association with these tests.

2. Methods

The study was approved by the Austin Health Human Research Ethics Committee (Study number HREC/94302/Austin2023) with waiver of informed consent.

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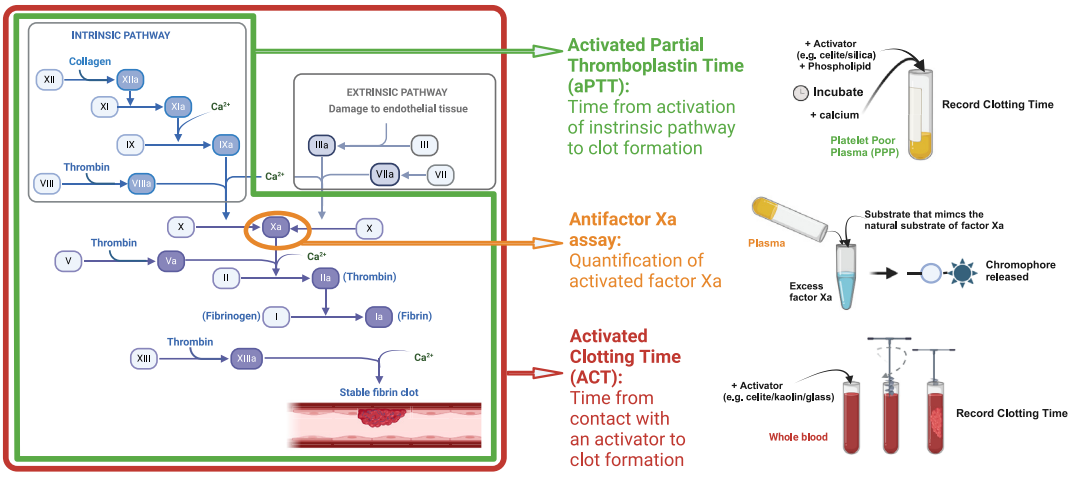

Fig. 1. aPTT, anti-Xa and ACT: three tests compared. The activated partial thromboplastin time (aPTT) measures the time necessary to generate fibrin from initiation of the intrinsic pathway when reagents are added to platelet poor plasma. To measure anti-Xa level, the patient's plasma is mixed with excess factor Xa. Heparin, if present, binds to antithrombin, forming a complex with factor Xa. The remaining factor Xa decreases as heparin increases. A substrate mimicking factor Xa's natural substrate is introduced, cleaved by residual factor Xa, releasing a colored compound (chromophore) detectable by a spectrophotometer. Chromophore quantity inversely correlates with heparin activity. Results are expressed as units/mL of anti-Xa activity. Activated clotting time (ACT) is measured by adding a known amount of activator to the patient's blood sample, initiating the coagulation cascade. A stopwatch is started, and the time it takes for clot formation to occur is recorded as the ACT value. Created with BioRender.com.

2.1. Inclusion criteria, exclusion criteria and data collection

We included simultaneous triple-paired samples collected from patients who received a UFH infusion while treated in the ICUs of the Austin Hospital between November 1, 2022 and March 1, 2023. Over this period, attending clinicians introduced a triple check to the monitoring of anticoagulation to establish greater safety, thus adding anti-Xa and ACT to the usual aPTT measurements. The protocol used to titrate the UFH infusion in our ICU according to aPTT and anti-Xa values is presented in Supplementary Material 1. We excluded patients <18 years old or those who received regional UFH infusion for the continuous renal replacement therapy circuit, antagonized by post-filter protamine.

Samples were collected simultaneously in two different tubes with citrate concentration of 0.109 mol/L (3.2%): one was sent to the laboratory for aPTT and anti-Xa activity and one was used for the thromboelastogram (TEG). We then undertook a retrospective assessment of the findings. Data collection included routinely collected demographic information, laboratory data for biochemistry and haematology and anti-coagulation results, as well as details of intravenous UFH therapy dose and duration.

2.2. Technical aspects of aPTT, anti-Xa and ACT measurements

aPTT measurements were conducted using the SynthASil reagent from HemosIL® (Instrumentation Laboratory Company - Bedford, MA, USA).

Anti-Xa measurements were conducted using the HemosIL® Liquid Anti-Xa assay (Instrumentation Laboratory Company - Bedford, MA, USA), which does not contain exogenously added antithrombin and contains dextran sulphate.[33]

ACT measurements were performed utilizing the TEG® 6s Global Hemostasis instrument from HAEMONETICS® with its citrated multi-channel cartridge.

2.3. Statistical analysis

We used descriptive statistics and applied Spearman's test to assess the correlation between aPTT, anti-Xa and ACT. We present such linear regressions in the results to make results understandable and comparable to previous papers' findings. However, as we performed several measurements in each patient, the correlation between the three variables was also assessed by linear mixed model analysis with patients as a random effect and a coefficient of determination (R-squared) computed using Zhang's method,[34] as reported in the supplementary material. Furthermore, we investigated concordance for values within defined therapeutic ranges for aPTT, ACT and anti-Xa. Additionally, factors associated with aPTT, anti-Xa and ACT were assessed using a multilevel linear mixed model with patients treated as a random effect. Variables included in the model were selected using the full pre-specification method.[35] The collinearity assumption was checked within the final models. A two-sided p-value <0.05 was considered statistically significant.

Finally, we performed the Wilcoxon signed rank test to compare the aPTT, anti-Xa and ACT at the time nearest to the bleeding episode in the patients who experienced such episodes with the worst values in those who did not experience bleeding episodes.

Statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) with the packages “tableone”, “ggpubr”, “ggplot2”, “dplyr”, “tidyverse”, “rsq” and “ggstatsplot”.[36]

2.4. Definitions

We defined different thresholds for each variable, identifying subtherapeutic, therapeutic and supratherapeutic ranges as previously published.

Thus, we defined a subtherapeutic range for aPTT at < 60 s, a therapeutic range at ≥ 60 s but ≤80 s and a supratherapeutic range at > 80 s. These values correspond to the mean of the lowest and highest values targeted for our patients and have been used in literature as reference values for therapeutic range.[37,38]

We defined a subtherapeutic range for anti-Xa levels of <0.3 units/mL according to the literature and our laboratory values, a therapeutic range for anti-Xa levels ≥0.3 units/mL but ≤0.7 units/mL and a supratherapeutic range for anti-Xa levels >0.7 units/mL.[37,39]

We defined a subtherapeutic range for ACT at < 152 s, a therapeutic range at ≥ 152 s but ≤200 s and a supratherapeutic range at

> 200 s, according to the normal range defined by TEG® 6s and the ACT target range for ECMO.[40]

We defined a Spearman correlation value of >90% as excellent, a value of <90% but >80% as very good, a value of <80% but >70% as good, a value of <70% but >60% as fair, a value < 60% but >50% as limited and a value < 50% as poor, in relation to this context.[41]

We chose the same thresholds to define the levels of concordance for subtherapeutic, therapeutic and supratherapeutic ranges of aPTT, anti-Xa and ACT. In addition, as sensitivity analysis, we investigated the concordance between the three variables according to the therapeutic range of aPTT ≥70 s but ≤110 s, as per our hospital protocol. This was done to assess the robustness of our findings. To assess the frequency of bleeding events in the patients included in our study, we considered any episode that was reported as "bleeding" in the clinical records.

Liver disease was determined by the presence of any grade of cirrhosis based on the clinical records.

3. Results

We studied 136 paired samples from 24 patients between the 1st of November 2022 and the 1st of March 2023. Patients' characteristics at baseline and admission are shown in Table 1. The median number of paired measurements for each patient was 4 [interquartile range (IQR) 3, 6]. The median UFH dose was 14.6 [IQR 10.5, 18.3] units/kg/h. The median APACHE III score was 50 [IQR 43–78]. None of our patients were on ECMO. The seven patients who had been receiving chronic anticoagulant therapy before ICU admission received their last dose at least 5 days before our sample collection.

Table 1
Baseline characteristics of study patients.

Characteristics on admission	Number: 24
Age (year)	60 [51, 66]
Male – *n* (%)	19 (79)
Body Weight (kg)	89 [75, 99]
Mechanical ventilation on admission – *n* (%)	19 (79)
APACHE III score	50 [43, 78]
aPTT (second)	36 [31, 39]
INR	1.3 [1.2, 1.4]
Hematocrit (%)	0.36 [0.31, 0.43]
Hemoglobin (g/L)	116 [101, 142]
Platelet count (*n*/mcL)	211,000 [170,250–270,500]
Fibrinogen (g/L)	4.90 [2.80, 5.50]
Past medical history	
Smoker – *n* (%)	5 (21)
Hypertension – *n* (%)	6 (25)
Diabetes – *n* (%)	8 (33)
Cardiovascular disease – *n* (%)	6 (25)
Chronic heart failure – *n* (%)	5 (21)
Cirrhosis – *n* (%)	2 (8)
Chronic Anticoagulant Therapy – *n* (%)	7 (29)
Chronic antiplatelet Therapy – *n* (%)	6 (25)
Clinical indication for heparin infusion	
Coronary/stent thrombus – *n* (%)	3 (12)
Dehiscence of aortic graft – *n* (%)	2 (8)
Limb ischemia – *n* (%)	4 (17)
Mechanical valve – (%)	3 (12)
Pulmonary embolism – *n* (%)	5 (21)
Venous thrombosis – *n* (%)	7 (29)
Reason for admission	
After cardiac or major vascular surgery – *n* (%)	5 (21)
Cardiogenic shock – *n* (%)	3 (12)
Septic shock – *n* (%)	4 (17)
Critical limb ischemia – *n* (%)	3 (12)
Other[a] – *n* (%)	9 (37)

Categorical variables presented as number with percentage in brackets, continuous variables presented as median with interquartile range.
aPTT: activated partial thromboplastin time; INR: international normalized ratio.
[a] Other reasons for admission: pulmonary oedema, pulmonary embolism, tracheal stenosis, acute liver failure, liver transplant, oesophagectomy, acute kidney injury requiring renal replacement therapy, cardiac arrest, renal mass with IVC thrombus.

3.1. Correlation between coagulation tests

Fig. 2a–c shows the correlation between aPTT, anti-Xa and ACT. The Spearman correlation coefficient was 0.71 between aPTT and anti-Xa (Fig. 2a). However, the correlation coefficient was only 0.42 between aPTT and ACT (Fig. 2b), and only 0.32 between ACT and anti-Xa (Fig. 2c). The results of the linear mixed model analysis confirmed these findings and are presented in Supplementary Material 2.

3.2. Concordance for therapeutic ranges

The therapeutic range concordance assessment between aPTT, anti-Xa and ACT for therapeutic values is shown in Fig. 3a–c.

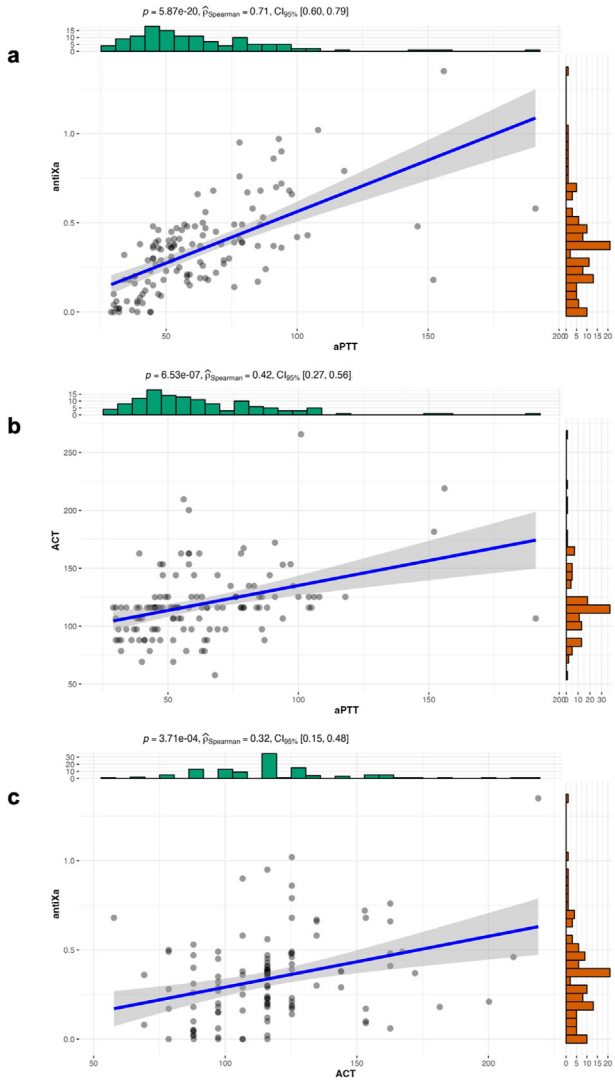

Fig. 2. (a–c) Correlation between aPTT, anti-Xa, and ACT. aPTT: Activated partial thromboplastin time; antiXa: anti-factor Xa levels; ACT: Activated Clotting Time; S: Spearman statistical test; *p*: *p*-value; Spearman *ρ*: Spearman's rank correlation coefficient; CI: confidence interval; top green histogram: histogram of the distribution of the x values; side orange histogram: histogram of the distribution of the y values.

When the aPTT was in the therapeutic range ($n = 29$), anti-Xa levels were also in the therapeutic range in 62% of cases.

Conversely, when the anti-Xa levels were in the therapeutic range ($n = 60$), the aPTT was also in the therapeutic range in 30% of cases (Fig. 3a).

When the aPTT was in the therapeutic range ($n = 29$), the ACT was also in the therapeutic range in only 10% of cases and subtherapeutic in 90%. Conversely, when the ACT was in the therapeutic range ($n = 14$), the aPTT was also in the therapeutic range in 21% of cases (Fig. 3b).

When the anti-Xa levels were in the therapeutic range ($n = 56$), the ACT was also in the therapeutic range in only 11% of cases, but it was subtherapeutic in 88%. Conversely, when the ACT was in the therapeutic range ($n = 13$), the anti-Xa levels was also in the therapeutic range in 46% of cases (Fig. 3c).

Following a sensitivity analysis with the therapeutic range of aPTT set between 70 and 110 s, as per our hospital protocol, only 39 (28.6%) samples were within this range. The concordance for therapeutic ranges between aPTT and anti-Xa was 64% when aPTT served as the standard and 35% when anti-Xa served as the standard. In contrast, the concordance between aPTT and ACT was 14% when aPTT served as standard and only 36% when ACT served as the standard.

An additional sensitivity analysis with the therapeutic range of aPTT set between 60 and 90 s did not materially alter our findings, as shown in Supplementary Material 3.

3.3. Concordance when two tests were in the therapeutic range

The therapeutic range concordance assessment for samples where two tests were simultaneously in the therapeutic range is shown in Supplementary Material 4. The simultaneous presence of two tests in the therapeutic range was always below 15%. When both the aPTT and anti-Xa levels were in the therapeutic range ($n = 17$; 12.5% of samples), the ACT was also in the therapeutic range in only 12% of samples. When the aPTT and ACT were in the therapeutic range ($n = 3$; 2.2% of samples), the anti-Xa levels were also in the therapeutic range in 67% of samples. When both anti-Xa levels and ACT were in the therapeutic range ($n = 6$; 4.4% of samples), the aPTT was also in the therapeutic range in 33% of cases.

3.4. Variables associated with coagulation test results

The complete results of the univariate and multivariate analysis are shown in Supplementary Material 5a–c. On multivariate analysis, aPTT was independently associated with UFH dose ($\beta = 1.8$ s

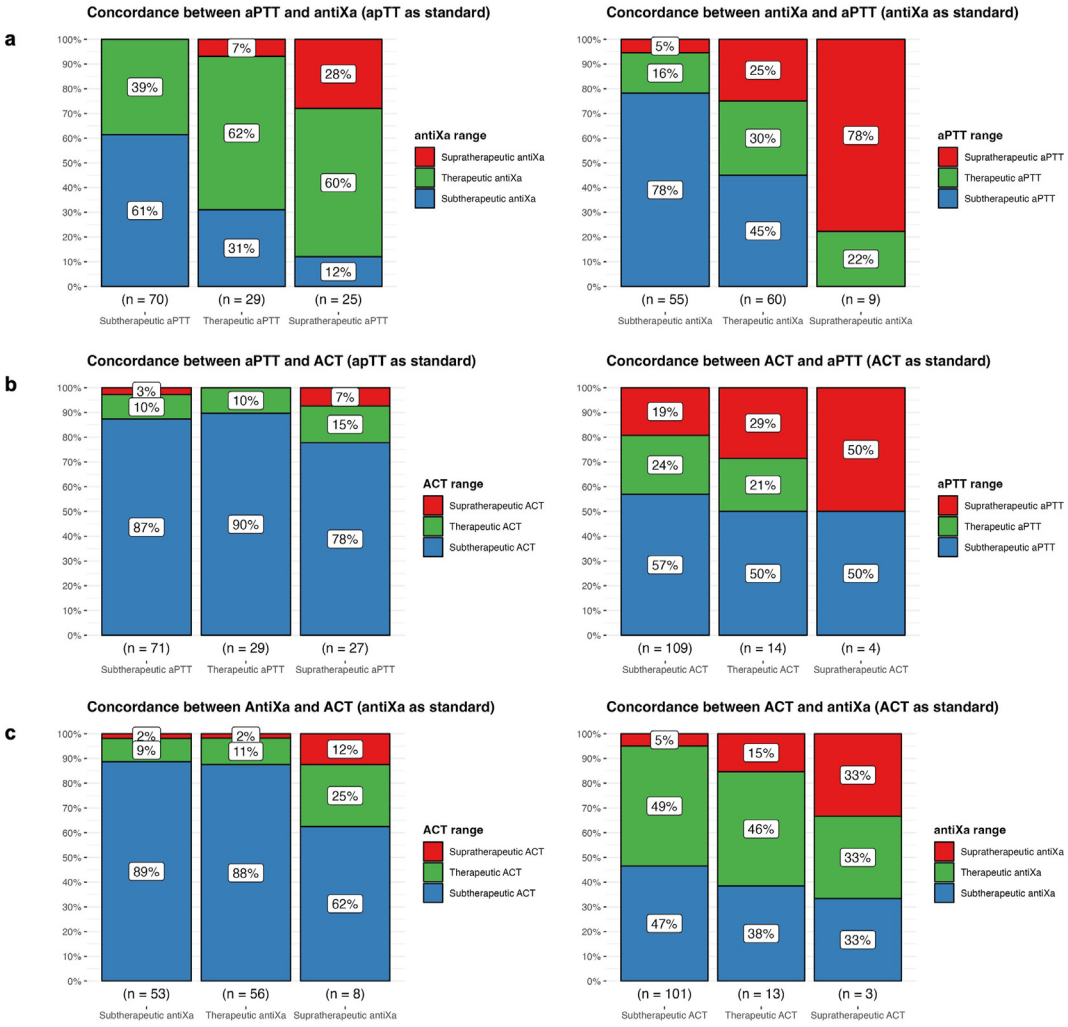

Fig. 3. (a–c) Concordance levels between aPTT, anti-Xa and ACT. aPTT: activated partial thromboplastin time; antiXa: anti-factor Xa levels; ACT: Activated Clotting Time.

[0.81, 2.7] per unit/kg/hour, $p < 0.001$), iCa ($\beta = -9$ s [−17, −0.94] per 0.1 mmol/L, $p = 0.029$), fibrinogen ($\beta = -8.7$ s [−16, −1.4] per g/L, $p = 0.02$) and platelet count ($\beta = 0.08$ s [00, 0.16] per 1×10^9/L, $p = 0.04$) (Supplementary Material 5a).

Similarly, anti-Xa was independently associated with UFH dose ($\beta = 0.02$ units/mL [0.01, 0.03] per unit/kg/hour, $p < 0.001$) and fibrinogen ($\beta = -0.07$ units/mL [−0.13, 0.00] per g/L, $p = 0.036$) (Supplementary Material 5b).

ACT was independently associated with UFH dose ($\beta = 1.1$ s [0.01, 2.3] per unit/kg/hour, $p = 0.048$), fibrinogen on the day of the sample collection ($\beta = -8.9$ s [−16, −2.0] per g/L, $p = 0.01$) and fibrinogen at admission to ICU ($\beta = 4.3$ s [0.03, 8.7] per g/L, $p = 0.049$). Of the three tests, ACT showed the least robust association with UFH dose (Supplementary Material 5c).

3.5. Bleeding complications and relationship to anticoagulation tests

Eight patients had at least one bleeding episode. Seven were minor (oral haemorrhage, epistaxis, oozing from the central venous line and arterial line, minor rectal bleeding). However, one patient required four red blood cell units for bleeding from the operation site on the third postoperative day after popliteal bypass surgery.

When patients with a bleeding episode were compared to those who did not have a bleeding complication, we found that the median values of aPTT and antiXa-levels nearest to the episode of bleeding were non-significantly lower than the median of the highest recorded value in those without a bleeding complication. We also found that the median ACT value nearest to the episode of bleeding was 111 [IQR 104–130] seconds, while the median of the highest recorded value in those without a bleeding complication was 158 s [IQR 116–164] ($p = 0.03$) (Supplementary Material 6(a-c)).

4. Discussion

4.1. Key findings

In a cohort of critically ill patients receiving UFH infusions, we studied the correlation and therapeutic range concordance of the three key tests used to monitor anticoagulation. We found that the correlation between anti-Xa and aPTT was just above fair and that the correlation between anti-Xa and ACT and between aPTT and ACT was poor. Furthermore, the simultaneous presence of two tests in the therapeutic range was uncommon. In addition, aPTT and anti-Xa were simultaneously in the subtherapeutic range in a minority of the cases. Sensitivity analysis using a different therapeutic range for aPTT did not materially alter our findings. All three tests were associated with heparin dose. However, in this setting, iCa, fibrinogen (both at baseline and on the day of sample collection) and platelet count demonstrated different independent associations with the three tests, even after adjusting for UFH dose. For instance, for every g/L increase in fibrinogen, the aPTT decreased by 8.7 s, anti-Xa by 0.07 units/mL and ACT by 8.9 s. Finally, bleeding episodes were uncommon, not related to aPTT and anti-Xa levels and paradoxically associated with lower ACT values.

4.2. Relationship to previous studies

The three tests that we studied have not been systematically and simultaneously compared before in a general population of critically ill patients receiving a continuous infusion of UFH.

However, during UFH infusion, Van Roessel et al. found that anti-Xa levels and aPTT therapeutic concordance occurred in 53% of cases.[42] Our findings of 43% concordance for therapeutic ranges are aligned with these findings.

Billoir et al. studied 107 samples from 30 ICU patients treated with UFH infusion and found that the correlation between aPTT and anti-Xa levels was only fair (Pearson r = 0.66). This finding is consistent with our observations.[43] Moreover, their therapeutic range concordance was even worse than in our study at only 7.5%. Arachchillage et al. analyzed 2836 paired aPTT and anti-Xa values from 250 critically ill adults receiving UFH. Most patients were supported by ECMO for severe respiratory or cardiac failure or both.[44] They found that therapeutic concordance was only 38%. Lardinois et al. assessed the correlation between a point-of-care aPTT ratio and anti-Xa levels from laboratory testing in 29 ICU patients.[45] The correlation coefficient between point-of-care aPTT ratio and anti-Xa levels was only 0.5 for the overall therapeutic range.

Nguyen et al. measured aPTT, anti-Xa, ACT and antithrombin levels in adult patients receiving UFH anticoagulation during extracorporeal membrane oxygenation (ECMO).[46] They found a fair correlation between aPTT values and anti-Xa levels (rho = 0.72), similar to that seen in our observations. In contrast, ACT exhibited a weak correlation with anti-Xa levels (rho = 0.33), a finding which is almost identical to our observations. However, these investigators did not provide information on therapeutic range concordance and they studied a unique population that was very different from ours.

More recently, Wehner et al. investigated the accuracy of two different ACT devices in monitoring low-dose UFH infusion in 60 critically ill patients.[11] They found no relationship between ACT and either UFH dose, aPTT or anti-Xa. No concordance data was provided for being in the therapeutic range. Moreover, the definition for low-dose UFH for inclusion of ICU patients was not provided in the methods. Of note, our ACT value is the TEG -ACT calculated from the R parameter for the RapidTEG™ tests, which uses tissue factor and kaolin to initiate clotting. A previous study reported that TEG 6s assays can effectively be used to monitor and quantify the effect of UFH,[47] although viscoelastic haemostatic assays were not designed for monitoring or guiding anticoagulation therapy.

4.3. Implications of study findings

Our findings imply that the tests routinely used in clinical practice to assess anticoagulation in critically ill patients undergoing UFH infusion have limited correlation and/or concordance for defined therapeutic ranges. Furthermore, they suggest that, compared with aPTT and anti-Xa activity, the ACT consistently underestimated the anticoagulation state of patients. In addition, our findings suggest that, although these tests are all correlated to the UFH dose, they can be influenced by several independent biochemical, haematological and clinical variables that are often altered in critically ill patients. Finally, these coagulation tests do not establish a distinct safety or efficacy threshold in ICU patients, it is not possible to recommend relying on one single test over the others. The association of these tests with UFH dose does not negate the influence of other variables, nor does it imply a correlation with the risk of bleeding or thrombosis due to the complexity of the haemostasis process. Additionally, interpreting multiple tests may not be beneficial when there is poor concordance within therapeutic ranges. Therefore, the clinical context and risk assessment should always be considered when monitoring such patients, and further research is needed comparing management with one test vs. another.

4.4. Study strengths and limitations

Our study has several strengths. First, it evaluates the correlation between the values generated by three common anticoagulation

tests in ICU patients as its primary focus. Moreover, the assessment of concordance for achieving a defined therapeutic range in ICU patients is presented for the first time for the three measurements together. Since no gold standard has been identified to monitor anticoagulation by UFH in critically ill patients, this comparison appears clinically relevant. Furthermore, the samples were collected simultaneously to minimize potential confounding factors. To ensure the accuracy of timing, we prospectively supervised the collection of the samples in accordance with clinical prescriptions. Finally, many factors were shown to be confounders or predictors for anticoagulation status in critically ill patients, thus providing useful information to clinicians.

We acknowledge some limitations. First, we included only a limited number of samples. However, such samples were collected rigorously, and, with >100 triple-paired samples, the primary objective of the assessment was clearly defined and achieved. Second, ours is a single-centre study, potentially limiting the external validity or generalizability to other settings. However, the patients included in our study represent a broad sample of ICU patients in terms of comorbidities and reasons for admission and the tests we report used laboratory technology, which is standardized and widely applied worldwide for such measurements. These factors lend a degree of external validity to our observations. Third, we did not measure acute phase confounders such as factor VIII and antithrombin. However, such measurements are not routine practice in ICU patients receiving UFH infusions. Fourth, we did not account for boluses and pauses in the UFH dose variable and considered only the dose of UFH administered at the time of sample collection. However, samples were collected 6 h after any variations in UFH infusion (such as boluses or pauses), following clinical practice. This timing should minimize their impact on the results. Finally, we have insufficient data to evaluate properly the risk of bleeding or thrombosis, which are the clinically relevant outcomes. Nevertheless, our results already indicate that ACT may not be a reliable test for bleeding prediction. Moreover, a more rigorous assessment involving hundreds of patients can only be justified if pilot data obtained in a comparison of coagulation testing such as ours indicates the need for such studies.

5. Conclusion

In a cohort of ICU patients receiving UFH infusion, aPTT, anti-Xa and ACT showed limited correlation and limited concordance for therapeutic range. Moreover, UFH dose was associated with the three tests, but several UFH-independent factors influenced these measurements. These observations imply that more and much larger prospective studies monitoring the occurrence of bleeding and thrombosis and the relationship between such events and the above tests are needed to establish optimal monitoring in this unique high-risk population.

Conflict of interest

In accordance with the principles of transparency, we wish to disclose a potential conflict of interest regarding the submission of our article to Critical Care and Resuscitation. The chief editor of the journal, Rinaldo Bellomo, is listed as a co-author on this manuscript. While we believe that this relationship does not compromise the impartiality of the review process, we acknowledge the possibility of perceived bias and assure that the research and its conclusions have been presented objectively and rigorously. We leave it to the editorial team to determine whether any additional steps are necessary to ensure the integrity and fairness of the peer review process.

Credit authorship contribution statement

Sofia Spano: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization. **Akinori Maeda**: Methodology, Investigation, Resources, Data Curation, Writing - Review & Editing. **Anis Chaba**: Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing - Review & Editing. **Glenn Eastwood**: Conceptualization, Methodology, Data Curation, Writing - Review & Editing, Supervision, Project administration. **Maninder Randhawa**: Investigation, Resources, Data Curation, Writing - Review & Editing. **Christopher Hogan**: Methodology, Resources, Writing - Review & Editing, Supervision. **Rinaldo Bellomo**: Conceptualization, Methodology, Writing - Review & Editing, Supervision. **Stephen Warrillow**: Conceptualization, Methodology, Writing - Review & Editing, Supervision.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2024.08.004.

References

[1] Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI. Parenteral anticoagulants: American college of chest physicians evidence-based clinical practice guidelines. Chest 2008;133(Suppl. 6):141S–59S.
[2] Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 2012;141(Suppl. 2):e24S–43S.
[3] Bloemen S, Hemker HC, Al Dieri R. Large inter-individual variation of the pharmacodynamic effect of anticoagulant drugs on thrombin generation. Haematologica 2013;98(4):549–54.
[4] Delavenne X, Ollier E, Chollet S, Sandri F, Lanoiselee J, Hodin S, et al. Pharmacokinetic/pharmacodynamic model for unfractionated heparin dosing during cardiopulmonary bypass. Br J Anaesth 2017;118(5):705–12.
[5] Olson JD, Arkin CF, Brandt JT, Cunningham MT, Giles A, Koepke JA, et al. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: laboratory monitoring of unfractionated heparin therapy. Arch Pathol Lab Med 1998;122(9):782–98.
[6] Smythe MA, Priziola J, Dobesh PP, Wirth D, Cuker A, Wittkowsky AK. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. J Thromb Thrombol 2016;41(1):165–86.
[7] Francis JL, Groce 3rd JB, Heparin Consensus G. Challenges in variation and responsiveness of unfractionated heparin. Pharmacotherapy 2004;24(8 Pt 2):108S–19S.
[8] Eikelboom JW, Hirsh J. Monitoring unfractionated heparin with the aPTT: time for a fresh look. Thromb Haemost 2006;96(5):547–52.
[9] Guervil DJ, Rosenberg AF, Winterstein AG, Harris NS, Johns TE, Zumberg MS. Activated partial thromboplastin time versus antifactor Xa heparin assay in monitoring unfractionated heparin by continuous intravenous infusion. Ann Pharmacother 2011;45(7–8):861–8.
[10] Hutt Centeno E, Militello M, Gomes MP. Anti-Xa assays: what is their role today in antithrombotic therapy? Cleve Clin J Med 2019;86(6):417–25.
[11] Wehner JE, Boehne M, David S, Brand K, Tiede A, Bikker R. Activated clotting time (ACT) for monitoring of low-dose heparin: performance characteristics in healthy adults and critically ill patients. Clin Appl Thromb Hemost 2020;26.
[12] Galli M, Angiolillo DJ. The evaluation and management of coagulopathies in the intensive therapy units. Eur Heart J Acute Cardiovasc Care 2023;12(6):399–407.
[13] Russell L, Madsen MB, Dahl M, Kampmann P, Perner A. Prediction of bleeding and thrombosis by standard biochemical coagulation variables in haematological intensive care patients. Acta Anaesthesiol Scand 2018;62(2):196–206.
[14] Vincent JL, Castro P, Hunt BJ, Jorres A, Praga M, Rojas-Suarez J, et al. Thrombocytopenia in the ICU: disseminated intravascular coagulation and thrombotic microangiopathies-what intensivists need to know. Crit Care 2018;22(1):158.
[15] Neuenfeldt FS, Weigand MA, Fischer D. Coagulopathies in intensive care medicine: balancing act between thrombosis and bleeding. J Clin Med 2021;10(22).
[16] Litton E. Treating intensive care anaemia to improve patient outcomes. Anaesthesia 2023;78(10):1203–5.
[17] Hof L, Choorapoikayil S, Meybohm P, Zacharowski K. Patient Blood Management in intensive care patients. Curr Opin Crit Care 2021;27(6):709–16.

[18] Thachil J, Warkentin TE. How do we approach thrombocytopenia in critically ill patients? Br J Haematol 2017;177(1):27–38.
[19] Levi M, Lowenberg EC. Thrombocytopenia in critically ill patients. Semin Thromb Hemost 2008;34(5):417–24.
[20] Zaloga GP. Hypocalcemia in critically ill patients. Crit Care Med 1992;20(2):251–62.
[21] Kelly A, Levine MA. Hypocalcemia in the critically ill patient. J Intens Care Med 2013;28(3):166–77.
[22] Melchers M, van Zanten ARH. Management of hypocalcaemia in the critically ill. Curr Opin Crit Care 2023;29(4):330–8.
[23] Du F, Jiang P, He S, Song D, Xu F. Antiplatelet therapy for critically ill patients: a pairwise and bayesian network meta-analysis. Shock 2018;49(6):616–24.
[24] Woznica EA, Inglot M, Woznica RK, Lysenko L. Liver dysfunction in sepsis. Adv Clin Exp Med 2018;27(4):547–51.
[25] Hoffman M. Coagulation in liver disease. Semin Thromb Hemost 2015;41(5):447–54.
[26] Uprichard J, Manning RA, Laffan MA. Monitoring heparin anticoagulation in the acute phase response. Br J Haematol 2010;149(4):613–9.
[27] Ali A, Mohan P, Kareem H, Muhammed MK. Elevated factor VIII levels and shortened APTT in recurrent abortions. J Clin Diagn Res 2016;10(1):EC04-6.
[28] Mitsuguro M, Okamoto A, Shironouchi Y, Sano M, Miyata S, Neki R, et al. Effects of factor VIII levels on the APTT and anti-Xa activity under a therapeutic dose of heparin. Int J Hematol 2015;101(2):119–25.
[29] Butenas S, van't Veer C, Mann KG. "Normal" thrombin generation. Blood 1999;94(7):2169–78.
[30] Suzuki K, Wada H, Matsumoto T, Ikejiri M, Ohishi K, Yamashita Y, et al. Usefulness of the APTT waveform for the diagnosis of DIC and prediction of the outcome or bleeding risk. Thromb J 2019;17:12.
[31] Ehrhardt Jr JD, Boneva D, McKenney M, Elkbuli A. Antithrombin deficiency in trauma and surgical critical care. J Surg Res 2020;256:536–42.
[32] Allingstrup M, Wetterslev J, Ravn FB, Moller AM, Afshari A. Antithrombin III for critically ill patients: a systematic review with meta-analysis and trial sequential analysis. Intens Care Med 2016;42(4):505–20.
[33] Lasne D, Toussaint-Hacquard M, Delassasseigne C, Bauters A, Flaujac C, Savard P, et al. Factors influencing anti-Xa assays: a multicenter prospective study in critically ill and noncritically ill patients receiving unfractionated heparin. Thromb Haemost 2023;123(12):1105–15.
[34] Zhang D. Coefficients of determination for mixed-effects models. J Agric Biol Environ Stat 2022;27(4):674–89.
[35] Leisman DE, Harhay MO, Lederer DJ, Abramson M, Adjei AA, Bakker J, et al. Development and reporting of prediction models: guidance for authors from editors of respiratory, sleep, and critical care journals. Crit Care Med 2020;48(5):623–33.
[36] Patil I. Visualizations with statistical details: the 'ggstatsplot' approach. J Open Source Softw 2021;6:3167.
[37] Samuel S, Allison TA, Sharaf S, Yau G, Ranjbar G, McKaig N, et al. Antifactor Xa levels vs. activated partial thromboplastin time for monitoring unfractionated heparin. A pilot study. J Clin Pharm Ther 2016;41(5):499–502.
[38] Barrett CD, Moore HB, Moore EE, Wang J, Hajizadeh N, Biffl WL, et al. Study of alteplase for respiratory failure in SARS-CoV-2 COVID-19: a Vanguard multicenter, rapidly adaptive, pragmatic, randomized controlled trial. Chest 2022;161(3):710–27.
[39] Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004;126(Suppl. 3):188S–203S.
[40] Extracorporeal life support organization guidelines for cardiopulmonary extracorporeal life support. 2017.
[41] Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. Anesth Analg 2018;126(5):1763–8.
[42] van Roessel S, Middeldorp S, Cheung YW, Zwinderman AH, de Pont AC. Accuracy of aPTT monitoring in critically ill patients treated with unfractionated heparin. Neth J Med 2014;72(6):305–10.
[43] Billoir P, Elie T, Levy JH, Besnier E, Dureuil B, Veber B, et al. Anticoagulation monitoring with activated partial ThromboPlastin time and anti-Xa activity in intensive care unit patients: interest of thrombin generation assay. Int J Mol Sci 2022;23(19).
[44] Arachchillage DRJ, Kamani F, Deplano S, Banya W, Laffan M. Should we abandon the APTT for monitoring unfractionated heparin? Thromb Res 2017;157:157–61.
[45] Lardinois B, Hardy M, Michaux I, Horlait G, Rotens T, Jacqmin H, et al. Monitoring of unfractionated heparin therapy in the intensive care unit using a point-of-care aPTT: a comparative, longitudinal observational study with laboratory-based aPTT and anti-Xa activity measurement. J Clin Med 2022;11(5).
[46] Nguyen TP, Phan XT, Huynh DQ. Monitoring unfractionated heparin in adult patients undergoing extracorporeal membrane oxygenation (ECMO): ACT, APTT, or ANTI-XA? Crit Care Res Pract 2021;2021:5579936.
[47] Dias JD, Lopez-Espina CG, Panigada M, Dalton HJ, Hartmann J, Achneck HE. Cartridge-based thromboelastography can be used to monitor and quantify the activity of unfractionated and low-molecular-weight heparins. TH Open 2019;3(3):e295–305.