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Pragmatic study of a thromboprophylaxis algorithm in critically ill patients with SARS-COV-2 infection

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Abstract

The optimal thromboprophylactic strategy for patients affected by Coronavirus disease 2019 (COVID-19) has been debated among experts. This study evaluated the safety and efficacy of a thromboprophylaxis algorithm. This was a retrospective, single-center study in critically ill patients admitted to the intensive care unit (University affiliated Hospital) for acute respiratory failure due to Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2). From March 16 to April 9, 2020, thromboprophylaxis was adjusted according to weight (control group, n = 19) and after this date, thromboprophylaxis depended on an algorithm based on thrombotic and hemorrhagic risk factors (protocol group, n = 13). With regard to safety (number of major bleeding events and blood transfusions), the groups were not significantly different. With regard to efficacy, the number of thrombotic events decreased from 37 to 0%, $p = 0.025$ after implementation of the algorithm. Also, peak fibrinogen dropped from 8.6 (7.2–9.3) to 6.5 (4.6–8.4) g/L, $p = 0.041$ and D-dimers from 2194 (1464–3763) to 1486 (900–2582) ng/mL, $p = 0.0001$. In addition, length of stay declined from 19 (10–31) to 5 (3–19) days, $p = 0.009$. In conclusion, a tailored thromboprophylaxis algorithm (risk stratification based on clinical parameters and biological markers) reduce thrombotic phenomena in critically ill COVID-19 patients without increasing major bleeding.

Keywords COVID-19 · SARS-CoV-2 · Anticoagulation · Thrombosis · Hypercoagulability

Highlights

- "COVID-19-associated coagulopathy" (CAC) is characterized by the development of thrombotic events.
- The frequency of thrombotic events in patients with COVID-19 is high.
- Major bleeding complications in patients infected with SARS-CoV-2 remain much less frequent.
- A tailored thromboprophylaxis algorithm (risk stratification based on clinical parameters and biological markers) reduced thrombotic complications of CAC without increasing major bleeding.

Introduction

In the practical advice for the prevention of thrombosis and the management of coagulation dysfunction associated with coronavirus disease 2019 (COVID-19), several experts used the terminology "COVID-19-associated coagulopathy" (CAC) [1, 2]. Clinically, CAC is distinguished by a hypercoagulable state leading to the development of thrombotic events (TE) [3–9]. One of the first provisional guidelines from medical societies and expert groups (posted online between March 25 and April 3, 2020) highlighted the importance of following standard hemostasis measurements. However, a year later, the evidence-based thromboprophylaxis

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approach for critically ill COVID-19 patients is still being developed [1, 10–13] and current recommendations are based on expert opinions (https://www.covid19treatmentguidelines.nih.gov/antithrombotic-therapy/).

In this setting, we have developed and implemented an algorithm that integrates biological and clinical factors with the aim of optimizing the anticoagulant management of patients severely affected by COVID-19 and admitted to the intensive care unit (ICU). The research statement was as follows: Is the use of an empiric thromboprophylaxis algorithm for critically ill COVID-19 patients effective on the basis of (a) clinically significant events (i.e., the number of TE documented based on radiological analysis and/or surgical exploration), (b) reduction in biological markers (i.e., the levels of D-dimers and fibrinogen in both groups), and (c) the number of adverse events, specifically major hemorrhagic events and blood transfusions?

Materials and methods

Study design

This was a retrospective study before/after implementation of a thromboprophylaxis protocol spread over a period of 3 months from March 16 to June 16, 2020, concerning 32 consecutive patients treated in the ICU at the Centre Hospitalier Universitaire Tivoli (CHU Tivoli), La Louvière, Hainaut, Belgium. This study was approved on July 29, 2020 by the ethics committee of the CHU Tivoli (number 1362). The creation of the thromboprophylaxis algorithm for patients with severe COVID-19 was based on available literature data with a cut-off date of April 05, 2020 [1, 3–6, 11–17]. Our algorithm was implemented on April 09, 2020 [1, 3–6, 11–25]. Thus, the control group (CG) included 19 patients and the protocol group (PG) comprised 13 patients. Patients who were treated before April 09, 2020 received standard or boosted prophylaxis with low molecular weight heparin (LMWH), this was the CG in our analysis. The standard prophylactic dose of LMWH corresponded to enoxaparin 4000 IU daily, subcutaneous (s.c.) if body weight (bw) was < 100 kg or 6000 IU daily, s.c. if bw was > 100 kg. If the patient was placed on invasive mechanical ventilation or high flow oxygen therapy, boosted prophylaxis was prescribed (according to bw) twice daily (b.i.d.). After April 09, 2020 all patients had targeted management of heparin therapy based on the algorithm. Patients treated exclusively according to our algorithm were the PG in our analysis (Fig. 1). For more detailed information about the practical use of the algorithm, refer to supplementary file "Online Resource 1".

Study population

Included patients were (a) adults (18 years and older), (b) admitted to the ICU, (c) with acute hypoxemic respiratory failure characterized by a PaO_2/FiO_2 ratio ≤ 150 mm Hg [26], and (d) SARS-CoV-2 viral infection confirmed by molecular reverse-transcription polymerase chain reaction (RT-PCR) using a swab sample from the respiratory tract [27]. For more detailed information about the standard treatment administered to the two groups and exclusion criteria, refer to supplementary files "Online Resources 2, 3".

Laboratory tests

All tests were performed in the hospital laboratory. The viscoelastic tests were performed on a ROTEM delta™ (Werfen, Instrumentation Laboratory, Bedford, MA, USA) according to the manufacturer's recommendations [28]. The ROTEM™ assays have been presented in detail elsewhere [19, 20, 29]. Biomarkers of disease progression included C-reactive protein, white blood cell (WBC) count, neutrophil count, lymphocyte count, and neutrophil-to-lymphocyte ratio (NLR) [30]. For more detailed information about other laboratory tests, the normal limits, and analysis thresholds, refer to supplementary file "Online Resource 4".

Baseline clinical characteristics

We collected basic demographic data and medically-confirmed co-morbidities from the computerized patient record. Multi-morbidity referred to the presence of ≥ 3 severe co-morbidities identified before admission to the ICU: arterial hypertension, cerebrovascular disease (stroke/transient ischemic attack), diabetes mellitus, chronic kidney disease > stage 3B [31], congestive heart failure, coronary disease (coronary artery bypass grafting and/or history of acute myocardial infarction), chronic obstructive pulmonary disease GOLD ≥ 2 [32], metastatic carcinoma, obesity (body mass index ≥ 35) [33]. We calculated PaO_2/FiO_2 ratio (first arterial blood gas analysis recorded during ICU admission) [26]. Finally, we calculated various scores, including the APACHE II score, the Sequential Organ Failure Assessment (SOFA) score [34], the disseminated intravascular coagulation score (DIC) [35, 36], and the IMPROVE bleeding risk score [22, 23]. The diagnosis of Acute Respiratory Distress Syndrome (ARDS) was made according to the Berlin

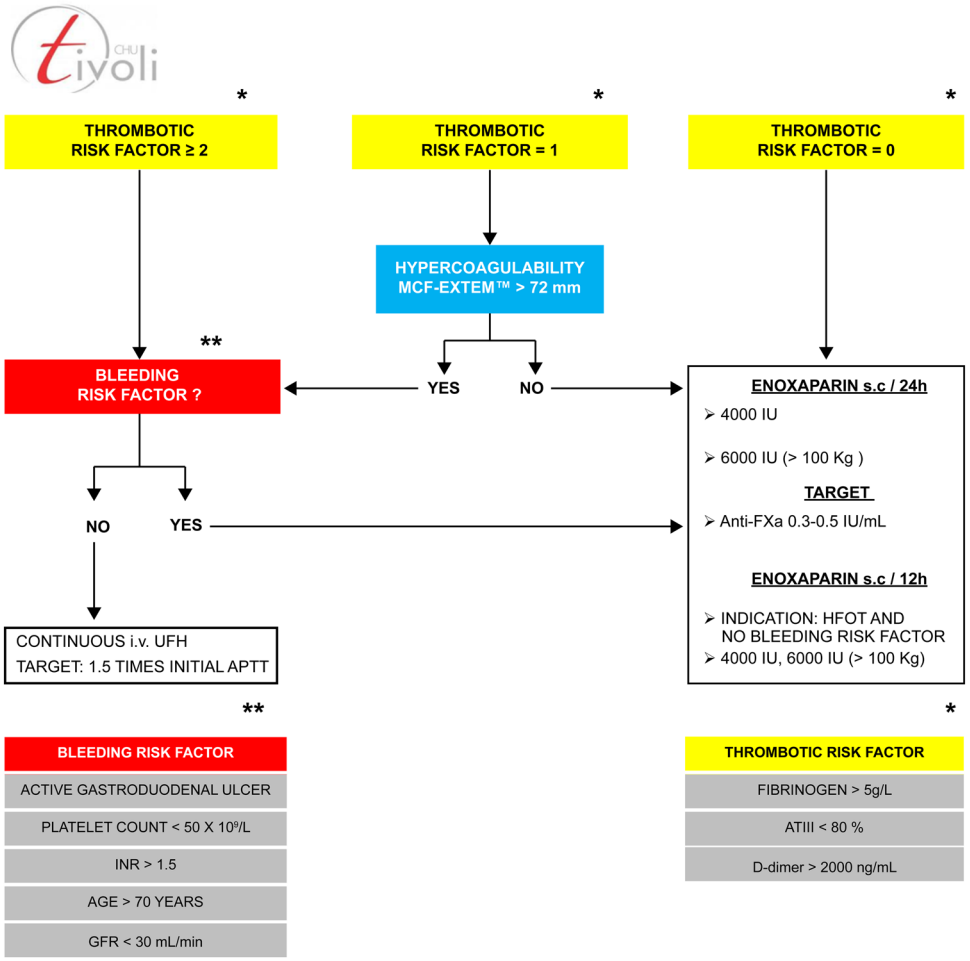

Fig. 1 Tailored thromboprophylaxis algorithm for the prevention of thrombotic events in critically ill COVID-19 patients. *Anti-FXa* anti-factor X activated, *APTT* activated partial thromboplastin time, *ATIII* antithrombin III, *GFR* glomerular filtration rate, *HFOT* high flow oxygen therapy, *ICU* intensive care unit, *INR* International Normalized Ratio, *i.v.* intravenous, *MCF-EXTEM*™ maximum clot firmness, *EXTEM*™ assay measured on rotational thromboelastometry, *s.c.* subcutaneous, *UFH* unfractionated heparin

definition [37]. Septic shock had been set according to the international definition for sepsis and septic shock (third consensus) [38]. Major bleeding was defined according to the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis (ISTH) [39].

Outcomes and clinical characteristics

We documented clinical characteristics and outcomes as follows: (a) invasive mechanical ventilation and acute renal replacement therapy via a continuous veno-venous hemofiltration program PRISMAFLEX ™ (Baxter, Brainel'Alleud, Belgium), (b) blood transfusions, (c) anti-coagulation regimens, (d) severe ARDS and septic shock and (e) TE (i.e., venous thromboembolism or arterial thrombosis), major bleeding and ICU mortality.

Statistical analyses

For comparisons of asymmetric variables, the Mann–Whitney (U) and Kruskal–Wallis (H) tests were used. For symmetric variables, Student's T (t) test and the Chi-square test (χ^2) were used for proportion comparisons. Statistical analyses were performed with Software for Statistics and Data Science (14.0, Texas, USA). Means and standard deviations ($\pm$) were used to describe symmetric variables. Median variables and Inter Quartile Range (IQR) were used to describe the asymmetric variables. Fisher's exact test was used when the frequencies were ≤ 5. A p value < 0.05 was considered statistically significant.

Results

Baseline characteristics at admission (Table 1)

There were no statistical differences between the groups in terms of demographic, clinical, and biological characteristics at baseline (Table 1). Fore more detailed information about characteristics, at baseline, in each group, refer to supplementary files "Online Resources 5–7".

Characteristics of the administered therapies (Table 2)

The CG and the PG were not significantly different with regard to the use of the UFH "moderate regimen", 37% vs 30% ($p = 1$). No patients were ineligible to receive continuous i.v. UFH due to a risk of bleeding to begin with, according to the bleeding risk factors described in the algorithm (Fig. 1). Overall, the CG and the PG were not significantly different with regard to blood transfusions.

Table 2 Characteristics of administered therapies

Characteristics	CG (n = 19)	PG (n = 13)	*p* value
UFH "moderate regimen"[a]	7 (37%)	4 (30%)	1
Combination ≥ 2 organ supports[b]	3 (16%)	3 (23%)	0.666
RBC transfusion, units	1 (0–1)	0 (0–1)	0.347
Platelet transfusion, units	0 (0–0)	0 (0–0)	N/A
FFP transfusion, units	0 (0–0)	0 (0–0)	N/A
RBC and PC and FFP transfusion, units	1 (0–1)	0 (0–1)	0.547
Patients transfused	10 (53%)	5 (38%)	0.490

Values are expressed as a number (%) or median (interquartile range)

CG control group, *N/A* not available, *PG* protocol group, *UFH* unfractionated heparin, *UFH* "moderate regimen" means a target 1.5 times the initial APTT

[a]Doses of UFH did not exceed 400 IU/Kg daily

[b]The combination of organ supports means the simultaneous presence of (i) invasive ventilation via trans-laryngeal intubation or tracheostomy or extracorporeal respiratory support, and (ii) acute renal replacement therapy via a continuous veno-venous hemofiltration program

Table 1 Demographic, clinical, and biological characteristics at baseline

Characteristics	CG (n = 19)	PG (n = 13)	*p* value
Age, years	61.8 ± 12.5	64.1 ± 14.8	0.629
Male sex	11 (58%)	11 (85%)	0.141
Co-morbidity ≥ 3[a]	5 (26%)	4 (31%)	1
PaO_2/FiO_2 ratio D + 1, mmHg	92 (65–100)	69 (55–81)	0.161
APACHE II score	17 (10–46)	17 (8–29)	0.331
SOFA score	4 (2–7)	4 (2–8)	0.218
IMPROVE bleeding risk score	7 (4–12)	7.5 (2.5–4)	0.480
Fibrinogen D + 1, g/L	4.9 (4.7–7.5)	4.5 (4.6–7.9)	0.208
ATIII activity D + 1, %[b]	66 (56–87)	94 (78–106)	0.090
D-dimers D + 1, ng/mL FEU	1847 (1443–4841)	1146 (88–2492)	0.265
C-reactive protein D + 1, mg/L	159 (97–269)	122 (57–197)	0.185
LOS (before ICU admission), days	1 (0–4)	2 (1–4)	0.442

Values are expressed as mean ± standard deviation, number (%), or median (interquartile range)

APACHE II acute physiology and chronic health evaluation II, *ATIII* antithrombin III, *CG* control group, *D + 1* day one after admission to intensive care unit, *FEU* fibrinogen equivalent units, *IMPROVE* international medical prevention registry on venous thromboembolism, *LOS* length of stay in a non-critical COVID-19 unit, PaO_2/FiO_2 the ratio of arterial oxygen partial pressure (PaO_2 expressed in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction), *PG* protocol group *SOFA score* sequential organ failure assessment score

[a]Multi-morbidity refers to the presence of ≥ 3 severe co-morbidities: arterial hypertension, cerebrovascular disease (stroke/transient ischemic attack), diabetes mellitus, chronic kidney disease > stage 3B, congestive heart failure, coronary artery disease (coronary artery bypass grafting and/or history of acute myocardial infarction), chronic obstructive pulmonary disease GOLD ≥ II, metastatic carcinoma, obesity (body mass index ≥ 35)

[b]ATIII activity was not measured in 4/19 CG and 8/13 PG patients (non-performance of measurements in 21% and 38% of CG and PG, respectively, was due to study protocol according to the algorithm)

Table 3 Clinical and biological measurements

Characteristics	CG (n = 19)	PG (n = 13)	*p* value
IMV, days	19 (7–42)	13(1–19)	0.199
IMV	13 (68%)	6 (46%)	0.055
ICU LOS, days	19 (10–31)	5 (3–19)	0.009
ISTH-DIC score ≥ 5	0 (0%)	0 (0%)	N/A
Fibrinogen peak, g/L[a]	8.6 (7.2–9.3)	6.5 (4.6–8.4)	0.041
ATIII activity, %	60.5 (41–125)	67 (18–98)	0.516
Anti-FXa activity, IU/mL	0.66 (0.39–0.73)	0.44 (0.30–0.65)	0.001
D-dimers, ng/mL FEU	2194 (1464–3763)	1486 (900–2582)	0.0001
ROTEM MCF-EXTEM™, mm	N/A	77 (69–82)	N/A
TE	7 (37%)	0 (0%)	0.025
Severe ARDS	9 (47%)	4 (31%)	1
Septic shock	3 (16%)	2 (15%)	1
Major bleeding	1 (5%)	2 (15%)	1
Mortality	4 (21%)	4 (31%)	0.683

Values are expressed as median (interquartile range) or number (%)

ARDS acute respiratory distress syndrome, *ATIII* antithrombin III, *Anti-FXa* anti-factor Xa, *CG* control group, *FEU* fibrinogen equivalent units, *ICU* intensive care unit, *IMV* invasive mechanical ventilation, *ISTH-DIC score* International Society for Thrombosis and Hemostasis-Disseminated Intravascular Coagulation score, *LOS* length of stay, *MCF* maximum clot firmness, *N/A* not available, *PG* protocol group, *TE* thrombotic events (TE corresponded to 1 pulmonary embolism, 2 splanchnic ischemias, 2 strokes, 1 renal infarction, and 1 splenic infarction)

[a]Fibrinogen peak corresponds to the highest value during the stay measured at least twice over a 24-h interval

Outcomes, clinical and biological characteristics (Table 3)

While there was a non-significant trend in shorter duration of invasive mechanical ventilation of 13 (1–19) vs 19 (7–42) days ($p = 0.199$), between the PG compared to CG, there were fewer patients on invasive mechanical ventilation 46% vs 68% ($p = 0.055$), respectively, while the ICU length of stay was statistically and remarkably shorter 5 (3–19) vs 19 (10–31) days ($p = 0.009$), respectively.

Regarding biological profiles, the fibrinogen peak, measured during the ICU stay, was associated with a significant difference between the CG and the PG, with 8.6 (7.2–9.3) vs 6.5 (4.6–8.4) g/L ($p = 0.041$), respectively. For more detailed information about the fibrinogen peaks in each group, refer to supplementary files "Online Resource 8, 9". The ATIII activities were not significantly different between the CG and the PG but below the lower limit of normality. However, D-dimers were statistically and remarkably lower, 1486 (900–2582) vs 2194 (1464–3763) ng/mL, between the PG and the CG ($p = 0.0001$), respectively. Similarly, measurements of anti-FXa activity (measured at peak, 4 h after administration) were significantly lower in the PG compared to the CG, 0.44 (0.30–0.65) vs 0.66 (0.39–0.73) IU/mL ($p = 0.001$), respectively. Nine patients in the PG underwent viscoelastic analyses according to the algorithm (Fig. 1). The MCF-EXTEM™ was measured at 77 (69–82) mm, outside the upper limit of normality. For more detailed information about the MCF-EXTEM™ measurements, refer to supplementary file "Online Resource 10".

Concerning outcomes, the number of TE was statistically different 37% vs 0%, between the CG and the PG ($p = 0.025$), respectively. Overall, the CG and the PG were not significantly different for the number of patients affected by major bleeding 5% vs 15% ($p = 1$), respectively. At the level of mortality, no statistical distinction could be identified between the CG and the PG, 21% vs 31% ($p = 0.683$), respectively.

Discussion

With regard to safety, the implementation of our algorithm did not increase major bleeding rate and our results were in line with previous observations [40, 41]. For example, in a retrospective study (n = 42 patients) from Pavoni et al. notwithstanding the use of the administered anticoagulation regimen (intermediate dose enoxaparin 4000 IU or 6000 IU if body mass index > 35, s.c., b.i.d., or therapeutic dose enoxaparin 100 IU/Kg s.c., b.i.d.), no major hemorrhagic event was observed [40]. The controlled study, before/after implementation of a "more aggressive" thromboprophylaxis

protocol, from Stessel et al. involved 72 patients treated preventively with LMWH: a group of 46 patients treated with a low-dose thromboprophylaxis regimen (control group, nadroparin 2850 IU/daily, s.c.) and a group of 26 patients treated with an intensified thromboprophylaxis protocol (intervention group, nadroparin 3800 IU b.i.d., s.c.). The authors reported only one episode of bleeding [41].

With regard to efficacy, our results were in line with observations from various studies focused on TE and higher intensity thromboprophylaxis in COVID-19 ICU patients [42–44]. Several multicenter studies have demonstrated the ineffectiveness of prescribed-dose-prophylactic LMWH in COVID-19 patients [42, 43]. In a retrospective single-center study (n = 188 patients), an escalated-dose thromboprophylaxis strategy was implemented according to D-dimer levels and clinical and biological parameters [44]. The use of high-intensity prophylaxis treatment (enoxaparin 40 mg b.i.d. in 75 patients) was associated with a lower incidence of TE (12.2%), without increasing major bleeding. According to Atallah et al. the lower rate of TE may be related to the implementation of their tailored thromboprophylaxis approach [44].

With regard to the results of biological measurements, we were also in accordance with numerous reports. First, ATIII activity was decreased well below the lower limit of normality which was close to the findings from various studies [3, 5, 6, 42, 45]. Second, the MCF- EXTEM™ assays were outside the upper limit of normality which corroborated the work of other investigators [46–56]. These observations remain to be confirmed and, the international multicenter observational ROHOCO study (ROtem analysis and standard coagulation tests in HOspitalized patients with COvid-19) has completed its patient recruitment phase and the trial results are pending (https://www.drks.de/drks_web/). Third, the results of this study are in line with current observations regarding the amplification of fibrinogen and D-dimer levels well beyond the limits of normality [3–6, 8, 42, 45, 57]. It appears that an increase in D-dimers and fibrinogen levels produces hypercoagulability leading to pulmonary micro-thrombi and poor clinical outcomes in COVID-19 patients [4, 5, 58, 59]. After implementation of the algorithm, the decreases in D-dimer levels and fibrinogen peaks as well as the trend toward shorter invasive mechanical ventilation duration and a statistically significantly shorter ICU length of stay, reinforced our conviction that a tailored anticoagulant algorithm (risk stratification based on clinical parameters and biological markers) could reduce thrombotic phenomena. This theory may correspond to a previously published report in critically ill COVID-19 patients [60]. In the first randomized controlled trial of anticoagulant therapy in patients with COVID-19 (n = 20 patients), Lemos et al. compared preventive or therapeutic anticoagulation in patients requiring invasive mechanical ventilation [58]. Administration of therapeutic-dose showed improvement in PaO_2/FiO_2 ratios after 7 and 14 days, decreased D-dimer levels, and, particularly, the number of ventilator-free days compared with prophylactic dose anticoagulation (15 [IQR 6–16] vs 0 [IQR 0–11] days, $p = 0.028$) [60, 61].

With regard to baseline thrombotic risk, it was also important to analyze the similarities between the compared groups, refer to supplementary files "Online Resources 5–7, 11".

With regard to undeniable limitations, this study was limited in its mono-centric design, small sample size, retrospective nature, and the possible interference of confounding variables. Other factors contributing to an underestimation or overestimation of an outcome could bias our assessment. For example, none of the TE had been diagnosed by computed tomography angiography, so events reports were potentially subject to reporting bias. Lastly, our algorithm was set up on April 09, 2020 systematically in all patients affected by COVID-19 admitted to the ICU. Therefore, patients included in the CG who were still being treated in the ICU also benefited from this algorithm from the above-mentioned date. This treatment bias (overlapping therapies) could have altered the results as reported by Stessel et al. [41].

Conclusions

Our observations show that implementation of a pragmatic and easy-to-use, tailored anticoagulant algorithm (risk stratification based on clinical parameters and biological markers) can reduce thrombotic phenomena. In terms of safety of care, the use of a supra-preventive heparin therapy strategy did not appear to be associated with higher rates of major bleeding or blood transfusions. Although it appears that supra-preventive heparin administration reduced thrombotic phenomena, it did not change mortality. It is clear that the true magnitude of this study must be considered in light of the undeniable limitations of its observations. The external validation of these results into current practice assumes large sample size, randomized studies with control groups and, at the time of the writing this manuscript, several randomized studies to assess the efficacy/safety of anticoagulant prophylaxis strategies in critically ill COVID-19 patients are currently recruiting participants [62].

Supplementary Information The online version of this article (https://doi.org/10.1007/s11239-021-02514-3) contains supplementary material, which is available to authorized users.

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Author contributions Study conception and design were performed by MF. Material preparation, data collection and analysis were performed by MF, JB, YB, SF, FB, DH, CB and AB. The first draft of the manuscript was written by MF and all authors commented on previous versions of the manuscript. Formal analysis was carried out by AB. All authors read and approved the final manuscript.

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Data availability On request, the authors have made these data available to the editors during the peer-review process.

Declarations

Conflict of interest The authors declare no conflicts of interest/competing interests. Authors declare to adhere to the minimum reporting guidelines hosted by the EQUATOR Network when preparing their observational study (STROBE statement).

Ethical approval This retrospective study, involving human participants, was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethics committee of the Centre Hospitalier Universitaire Tivoli, La Louvière, Hainaut, Belgium (Université Libre Bruxelles, Bruxelles, Belgium) approved this study on July 29, 2020 (Number 1362).

Informed consent Formal informed consent was exempted by the ethics committee of our hospital due to the retrospective nature of the study and given the risks of awakening a painful past or of calling on a family to process data from a deceased person. No patient expressed opposition to the use of their medical records for research and/or publication purposes. This wish was respected by checking in each computerized medical file whether an objection form was archived in the "clinical research" section.

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