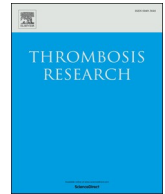




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Full Length Article

Venous thromboembolism and bleeding in critically ill COVID-19 patients treated with higher than standard low molecular weight heparin doses and aspirin: A call to action

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ABSTRACT

Background: Critically ill COVID-19 patients have a clear pattern of inflammation and hypercoagulable state. The main aim of the study was to evaluate the outcome of severe COVID-19 patients basing on prothrombotic risk factors (i.e. D-dimer). We also evaluated the impact of different doses of low molecular weight heparin (LMWH) on the incidence of bleedings.

Methods: The data of forty-two patients admitted to the Intensive Care Unit (ICU) were retrospectively analyzed. On ICU admission, patients with D-dimer < 3000 ng/mL (Group 1) received enoxaparin 4000 UI (6000 UI, if body mass index > 35) subcutaneously b.i.d. and patients with D-dimer ≥ 3000 ng/mL (Group 2) received enoxaparin 100 UI/kg every 12 h. Aspirin was administered to all patients once a day.

Results: Both groups presented a high incidence of perivascular thrombosis (40.9% in Group 1 and 30% in Group 2). Patients of Group 2 suffered a higher incidence of venous thromboembolism (VTE) than Group 1 (65% vs 13.6%, $p = 0.001$). One patient (4.5%) of Group 1 and three patients (15%) of Group 2 suffered from minor bleeding; no patient had major bleeding. Group 2 had a longer ICU and hospital stay than Group 1 (11.5 ± 5.6 vs 9.0 ± 4.8 and 30 ± 4.9 vs 21 ± 2.3 , $p < 0.05$, respectively) as well as increased ICU mortality (25% vs 9.1%).

Conclusions: More severe critically ill COVID-19 patients have a high incidence of VTE and worse outcome, despite the use of heparin at the therapeutic dose. However, the use of heparin did not increase the incidence of bleeding complications.

1. Introduction

Coronavirus disease 2019 (COVID-19) had been suggested to be caused by the upregulation of pro-inflammatory cytokines [1]. Protein mediators of inflammation, including Tumor Necrosis Factor (TNF), Interleukin 6 (IL-6) and Interleukin 8 (IL-8), promote thrombosis. Thrombin can trigger an inflammatory response in endothelial cells, platelets, and smooth muscle cells. In the presence of thrombosis, circulating IL-6 rises and increases liver production of fibrinogen, plasminogen-activator inhibitor, and C-reactive protein; in the same way, thrombin stimulates multiple pro-inflammatory cytokines in human vascular smooth muscle cells [2]. Clinical evidence and emerging data from radiological examinations indicate a high incidence of thrombotic complications in critically ill and non-critically ill COVID-19 patients

[3–5].

Some studies [6,7] have suggested that anticoagulant therapy with heparin reduces the inflammatory response because thrombosis and inflammation are closely interconnected. Recent data in an Italian population [8] showed that an increase of thromboprophylaxis with LMWH 6000 b.i.d. (8000 b.i.d. if body mass index > 35) plus clopidogrel loading dose 300 + 75 mg/day (if platelet count > 400,000 cells/ μ L), was associated with a significant time-related decrease of fibrinogen levels, D-dimer and pro-coagulant profile. Tang et al. [9] found that low molecular weight heparin (LMWH) or unfractionated heparin (UFH) at prophylactic dose was associated with a reduced 28-day mortality in COVID-19 patients with sepsis induced coagulopathy (SIC) score ≥ 4 or D-dimer levels ≥ 6 fold the upper limit of normal.

In 2016, the International Guidelines for management of sepsis and

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septic shock [10], recommended pharmacologic thromboprophylaxis with LMWH in hospitalized septic patients, while the guidelines on the management of critically ill patients with coronavirus disease 2019 [11] do not mention thromboembolic prophylaxis. Recently [12], a panel of experts and physicians from China and Europe developed an evidence and opinion-based consensus on the prophylaxis and management of venous thromboembolism (VTE) associated with COVID-19; the authors recommend pharmacological prevention with LMWH (i.e. 4000 IU of enoxaparin or 2850 IU of nadroparin once per day and adjusted dose for overweight or obese patients) as first line treatment in severe or critically ill COVID-19 patients. On the same line were the recommendations of the World Health Organization [13]. Currently, given the ongoing epidemic, the lack of clinical evidence has made it challenging to develop international guidelines. Therefore, we conducted a retrospective analysis of critically ill patients with COVID-19 pneumonia to evaluate the outcome of two different patient populations basing on D-dimer value on admission. The second aim of the study was to establish the incidence of derangement of the coagulation process and complications according to the severity of illness and the anticoagulant therapy.

2. Methods

2.1. Patients and data collection

A single-center, retrospective, observational study was done in the Anesthesia and Intensive Care Unit (ICU), Santa Maria Annunziata Hospital (Bagno a Ripoli, Tuscany, Italy), which is one of the designated hospitals in the region of Tuscany to treat patients with COVID-19 pneumonia. Forty-two adult patients (≥ 18 years old) admitted to the ICU because of COVID-19 pneumonia were retrospectively evaluated. Patients at time of admission already on vitamin K antagonists (AVK), direct oral anticoagulants (DOAC), or antiplatelet treatment with known bleeding diathesis or coagulation disorders were not included in the present study.

The diagnosis of severe COVID-19 pneumonia was according to World Health Organization (WHO) [13] interim guidance and was confirmed by two consecutive qualitative Reverse Transcription Polymerase Chain Reaction (RT-RNA) tests on a nose/throat swab positive for COVID-19 in the clinical laboratory of Santa Maria Annunziata Hospital (Bagno a Ripoli, Italy).

The Ethics Commission of Area Vasta Centro (Tuscany, Italy) approved this retrospective study. Written informed consent was waived due to the emergence of this infectious disease in Italy.

Demographic and clinical information were collected, including age, gender, body mass index (BMI), preexisting conditions (diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease, obesity), onset of symptoms to hospital admission and to ICU admission, Sequential Organ Failure Assessment (SOFA) on ICU admission, $\text{PaO}_2/\text{FiO}_2$ on ICU admission, need for non-invasive ventilation or mechanical ventilation, total length of ICU and hospital stay, and ICU and hospital mortality. The Sepsis Induced Coagulopathy (SIC) score system including PT, platelet count and SOFA was calculated and a SIC criteria total score ≥ 4 was considered, as suggested by the International Society of Thrombosis and Haemostasis (ISTH) [14].

Based on previous studies [9,15] that found a different outcome for different D-dimer values, patients were divided into two groups upon admission to the ICU: a first group with D-dimer < 3000 ng/mL that received intermediate dose (Group 1) (enoxaparin 4000 UI or 6000 UI, if body mass index > 35 , subcutaneously every 12 h) and a second group with a D-dimer ≥ 3000 ng/mL that received a therapeutic dose (Group 2) (enoxaparin 100 UI/kg b.i.d.). Aspirin (100 mg) was administered to all patients once a day.

During the study period, as required by the internal ICU protocol, in-patients with acute kidney injury (AKI), according to KDIGO definitions [16], the anti-Xa monitoring was performed. A therapeutic level

of 0.5–0.7 IU/mL of anti-Xa activity was considered [17]. Moreover, in case of a decrease in platelet count at $> 50\%$ of the basal value, the 4T score was used for diagnosis of heparin-induced thrombocytopenia (HIT) [18]; for each patient, the Padua prediction score was also calculated [19]. A cumulative score of 4 or more was defined as a high risk of VTE.

All patients underwent a therapeutic protocol, shared by a multi-disciplinary team composed of infectious disease specialists and pharmacologists, on the day of the hospital admission and throughout the hospital stay.

2.2. Thrombotic and bleeding events

The incidence of thrombotic and bleeding events was assessed.

Upon admission and at five days, bilateral extended compression ultrasound (ECUS) from the common femoral vein through the popliteal vein up to the calf veins confluence was performed in each of the included patients, using GE Logiq-e1 Vision scanner (GE, Healthcare, Italy). Deep vein thrombosis (DVT) was classified into 2 types: proximal (i.e. femoral and popliteal veins) and distal [i.e. posterior tibial veins, peroneal veins, anterior tibial veins, and muscular calf veins (soleal or gemellar veins)]. At the same time, ultrasound screening was helpful for detecting catheter-related venous thrombosis.

Patients with suspected symptomatic VTE, based on clinical signs (worse $\text{PaO}_2/\text{FiO}_2$ despite prone positioning or hemodynamic impairment requiring fluid challenge and/or increased norepinephrine infusion rate) received a computed tomography pulmonary angiography (CTPA), either at the admission to the ICU or during their stay. When established, pulmonary embolism was classified as truncular, lobar, segmental or sub-segmental, based on the location of the luminal defect.

If the patient was not transportable a transthoracic echocardiography was performed to identify indirect cardiac signs of pulmonary embolism as well as pulmonary arterial hypertension.

According to the Control of Anticoagulation Subcommittee [20], major bleeding events were based on the presence of symptomatic bleeding in a critical area or organ, such as intracranial, intraarticular, intraabdominal or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 2 g/dL or leading to transfusion of two or more units of whole blood or red cells. Minor bleeding was defined as unexpected hematoma > 25 cm², spontaneous nose-mouth bleeding > 5 min, macroscopic hematuria, airway bleeding and hematemeses [21].

2.3. Statistics

The results were expressed as mean \pm standard deviation or number (percentage), wherever appropriate. Normally distributed data were compared by Student's *t*-tests. Categorical variables were compared using the chi-squared test. A *p* value of < 0.05 was considered statistically significant. SPSS software version 25.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

3. Results

Forty-two patients (27 males, 15 females) were considered in the study. 16 (38%) suffered from two chronic underlying diseases, and 15 (35.7%) had three, mainly including hypertension [16 (38%)], obesity [16 (38%)], and diabetes [15 (35.7%)]. Twenty-three (54.8%) patients underwent mechanical ventilation and 19 (45.2%) non-invasive ventilation. Of the 42 patients that were included, 32 (76.2%) had a Padua risk score more than 4 and 10 (23.8%) had a risk score of 4. Ninety-two percent of patients received antivirals, 94% were prescribed an antibiotic therapy. Tocilizumab was administered to 25% of the patients, while corticosteroids were given to 45% of the cases.

At admission to the ICU, 22 (52.3%) patients received

Table 1

Demographical and clinical characteristics of COVID-19 pneumonia patients stratified on D-dimer value [Group 1 (D-dimer < 3000 ng/mL), Group 2 (D-dimer ≥ 3000 ng/mL)].

	Total patients n = 42	Group 1 n = 22 (52.3%)	Group 2 n = 20 (47.6%)	p value
Age (years)	64.3 ± 12.1	60 ± 14.4	64.8 ± 7.8	0.150
Sex				
Male, n (%)	27 (64.3)	16 (72.7)	11 (55)	0.231
Female, n (%)	15 (35.7)	6 (27.3)	9 (45)	
BMI, kg/m ²	27.5 ± 3.5	26.8 ± 3.8	31.4 ± 6.8	0.174
Comorbidities, n (%)	29 (69)	12 (54.5)	17 (85)	0.032*
Hypertension	16 (38)	5 (22.7)	11 (55)	0.314
Diabetes	15 (35.7)	6 (27.2)	9 (16.4)	0.231
Cardiovascular disease	6 (14.3)	2 (9)	4 (20)	0.312
COPD	5 (11.9)	5 (22.7)	0	0.022*
Obesity	16 (38)	5 (22.7)	11 (55)	0.031*
Onset of symptoms to				
Hospital admission (days)	6.2 ± 3.0	6.8 ± 2.8	4.6 ± 3.2	0.072
ICU admission (days)	8.6 ± 3.8	9.5 ± 2.4	7.4 ± 5.2	0.273
SOFA score on ICU admission	4.5 ± 0.9	4.1 ± 0.6	5.5 ± 1.1	0.020*
PaO ₂ /FiO ₂ on ICU admission	104.8 ± 13.3	117.5 ± 16.7	102.3 ± 12.2	0.197
Non invasive ventilation, n (%)	19 (45.2)	17 (77.3)	2 (10)	0.016*
Mechanical ventilation, n (%)	23 (54.8)	5 (22.7)	18 (90)	0.001*
Padua prediction score ≥ 4, n (%)	42 (100)	22 (100)	20 (100)	–

BMI: body mass index; COPD: chronic obstructive pulmonary disease; ICU: Intensive Care Unit; SOFA: Sequential Organ Failure Assessment.

Data are expressed by mean ± SD or number (percentage).

* p < 0.05.

anticoagulation with intermediate dose (Group 1) and 20 (47.6%) patients received a therapeutic dose (Group 2). SOFA score was higher in patients of Group 2 than patients of Group 1 (5.5 ± 1.1 vs 4.1 ± 0.6, p = 0.02). More patients of Group 2 underwent mechanical ventilation than Group 1 (90% vs 22.7%, p = 0.001). The demographic and clinical characteristics of the studied population are reported in Table 1.

Among the laboratory parameters only IL-6 was significantly higher in Group 2 than Group 1 (157.6 ± 83.7 vs 27 ± 6.9, p = 0.046). None of patients met SIC and HIT criteria. No patients suffered of AKI. Major laboratory markers are shown in Table 2.

One patient (4.5%) of Group 1 and 3 (15%) of Group 2 suffered from minor bleedings; two patients of Group 2 had airway bleedings and one patient of Group 1 and one of Group 2 presented macroscopic hematuria. No patients suffered from major bleedings.

Both groups presented a high incidence of catheter-related venous thrombosis (40.9% in Group 1 and 30% in Group 2). Ten thrombosis cases (23.8%) were associated with an internal jugular catheter and one (2.4%) with a subclavian catheter; four thromboses (9.5%) occurred

with a catheter placed in the femoral vein (Table 3). Patients of Group 2 suffered from a higher incidence of VTE than Group 1 (65% vs 13.6%, p = 0.001). Proximal DVT occurred in 13 patients (30.9%). Three symptomatic patients (7.1%) showed segmental pulmonary embolisms (1 of Group 1 and 2 of Group 2) (Table 3).

4. Discussion

Based on risk factors (i.e. D-dimer), our observational study suggests that the severe form of COVID-19 infection in critically ill patients has a clear pattern of inflammation and hypercoagulability with progression to organ failure, worsening the outcome in term of mortality and length of ICU stay. Our results showed an ICU mortality rate of 25% and it was likely determined by the different categorization of patients based on risk factors. According to recent evidences [9,15], we stratified patients on D-dimer value (high risk with D-dimer ≥ 3000 ng/mL and low risk with D-dimer < 3000 ng/mL). Patients identified as high risk had more comorbidities, including increased rates of obesity and inflammation

Table 2

Laboratory characteristics of COVID-19 pneumonia patients stratified on D-dimer value [Group 1 (D-dimer < 3000 ng/mL), Group 2 (D-dimer ≥ 3000 ng/mL)].

	Total patients n = 42	Group 1 n = 22 (52.3%)	Group 2 n = 20 (47.6%)	p value
Hb (g/dL)	10.8 ± 2.0	11.4 ± 2.4	10.2 ± 2.3	0.460
Leukocytes, × 10 ⁹ per L	6.4 ± 2.6	6.36 ± 2.3	6.5 ± 2.7	0.982
Platelet count, × 10 ⁹ per L	243.1 ± 149.3	206.2 ± 77.3	276 ± 177.7	0.228
Prothrombin time (PT), ratio	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	0.268
Activated partial thromboplastin time (aPTT) (s)	30.1 ± 3.7	31.6 ± 2.6	27.8 ± 4.5	0.202
ATIII (%)	77.5 ± 16.1	79.8 ± 23.5	73.4 ± 13	0.645
Fibrinogen (mg/dL)	> 700	> 700	> 700	–
IL-6 (pg/mL)	93.5 ± 87.7	27 ± 6.9	157.6 ± 83.7	0.046*
C-reactive protein (mg/L)	18.1 ± 9.2	13 ± 9	19.8 ± 9.2	0.334
Creatinine (mg/dL)	0.8 ± 0.3	0.82 ± 0.2	0.98 ± 0.3	0.510
Troponin T (pg/mL)	11.2 ± 6.8	7.8 ± 3.8	13.4 ± 7.4	0.288
LDH (U/L)	382 ± 111	364 ± 68	418 ± 158	0.436
Bilirubin (mg/dL)	1.1 ± 0.5	0.8 ± 0.3	1.1 ± 0.5	0.550
Procalcitonin (µg/L)	0.6 ± 1.9	0.4 ± 0.5	0.9 ± 1.7	0.456
SIC score (≥ 4), n patients	0	0	0	–

Hb: hemoglobin; ATIII: antithrombin III; IL-6: interleukin-6; LDH: lactate dehydrogenase; SIC: sepsis induced coagulopathy.

Data are expressed by mean ± SD or number.

* p < 0.05.

Table 3

Outcome measures of studied population stratified on D-dimer value [Group 1 (D-dimer < 3000 ng/mL), Group 2 (D-dimer ≥ 3000 ng/mL)].

	Total patients n = 42	Group 1 n = 22 (52.3%)	Group 2 n = 20 (47.6%)	p value
Length of ICU stay (days)	11.8 ± 5.1	9.0 ± 4.8	11.5 ± 5.6	0.040*
Length of hospital stay (days)	30 ± 4.9	21 ± 2.3	30 ± 4.9	0.002*
ICU mortality, n (%)	7 (16.7)	2 (9.1)	5 (25)	0.167
Hospital mortality, n (%)	9 (21.4)	4 (18.1)	5 (25)	0.590
Minor bleedings, n (%)	4 (9.5)	1 (4.5)	3 (15)	0.249
Airway bleedings, n (%)	2 (4.7)	0	2 (10)	
Macroscopic hematuria, n (%)	2 (4.7)	1 (4.5)	1 (5)	
Major bleedings, n (%)	0	0	0	–
VTE, n (%)	16 (38)	3 (13.6)	13 (65)	0.001*
PE, n (%)	3 (7.1)	1 (4.5)	2 (10)	
Proximal DVT, n (%)	13 (30.9)	2 (9.1)	11 (55)	
Perivascular thrombosis, n (%)	15 (35.7)	9 (40.9)	6 (30)	0.461
Internal jugular vein, n (%)	10 (23.8)	6 (27.3)	4 (20)	
Subclavian vein, n (%)	1 (2.4)	1 (4.5)	0	
Femoral vein, n (%)	4 (9.5)	2 (9.1)	2 (10)	

ICU: Intensive Care Unit; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis.

Data are expressed by mean ± SD or number (percentage).

* p < 0.05.

(high IL-6) compared to low risk patients. Moreover, they had significantly higher lengths of stay in both the ICU and hospital than low risk patients (11.5 ± 5.6 vs 9.0 ± 4.8 and 30 ± 4.9 vs 21 ± 2.3, p < 0.05, respectively).

Heparin seems to have a biological basis as a modulator of inflammation through four ways: 1. inhibits the activation of neutrophils; 2. interacts with the vascular endothelium to prevent the expression of inflammatory mediators which initiate and drive activation of the immune system; 3. inhibits proliferation of the vascular smooth muscle cells; 4. inhibits inflammation via its anticoagulant activity: a fall in thrombin formation in turn reduces adhesion molecules as well as platelet activation [22].

In the literature there are no high-quality data yet supporting early use of LMWH at a therapeutic dose in patients with COVID-19, outside the setting of VTE treatment; randomized controlled studies evaluating this question are planned [23] or open to recruitment (NCT04362085, NCT04345848, NCT04359277) or performed in a low number of patients [24]. In a French study conducted by Llitjos et al. [24] in which there were included 26 critically ill patients with severe COVID-19 pneumonia, the anticoagulation dose (prophylactic or therapeutic) was chosen at the discretion of the treating physician based on the individual risk of thrombosis; the authors found no difference within groups, suggesting that therapeutic dose could be unjustified. Moreover, in our study, in patients with D-dimer less than 3000, to whom we administered an intermediate dose of heparin, we found a mortality rate lower than in patients treated with prophylactic dose of French study (9.1% vs 12%). Similar to our study, Tang et al. [9] stratified patients basing on D-dimer value. They found a higher mortality rate in heparin users than in our patient population (32.8% vs 25%) for severe COVID-19 patients with a D-dimer > 3000 ng/mL. However, the authors had used heparin treatment with a prophylactic dose.

The overall incidence of venous thromboembolic events (perivascular thrombosis, DVT and PE) was considerable in our patient population (38%); moreover, it was statistically significantly higher in patients of Group 2 compared to Group 1. The total incidence of PE was 7.1%. These results are different from those of a recent study in 184 ICU patients that reported an ultrasonography VTE in 27% of patients; moreover, PE was the most frequent thrombotic complication (81%) [3].

The higher mortality in our population than in the literature [15,24] could be linked to the presence of microvascular thrombosis which cannot be diagnosed with instrumental investigations. An anatomic study [25] documented that at least some COVID-19 patients who become critically ill suffer from a generalized thrombotic microvascular

injury. Such pathology involves the lungs and appears mediated by intense complement activation.

Despite the use of therapeutic anticoagulation, no major hemorrhagic events, and no signs of SIC occurred; this highlights the possible safety even of high anticoagulant dose in these patients where the thromboembolic risk may exceed the bleeding risk.

In conclusion, risk stratification based on D-dimer values is fundamental in critically ill patients with COVID-19: high-risk patients are more severe due to a hyperinflammation state, have higher incidence of thromboembolic events and worse outcome compared with low risk ones. This aspect may have justified the use of heparin in therapeutic doses which, however, did not lead, at least in our patient population, to an increase of bleeding risk.

It seems appropriate to underline some limitations: first, this is a single-center study and the data on the influence over time of anticoagulant therapy on pro-inflammatory cytokines and fibrinolysis parameters, is missing. Second, it is not possible to draw definitive and certain conclusions about the efficacy of a high dose of LMWH on outcomes because the studied groups had a different severity of illness. Third, we decided to not include patients admitted to the ICU with COVID-19 and treated with VKA or DOAC due to the interference on the monitoring of coagulation parameters on ICU admission.

Further randomized controlled studies and immunological research will be able to clarify what is the “ideal” anticoagulant and at what dosage, for the treatment of severe hypercoagulable state in critically ill COVID-19 patients.

CRedit authorship contribution statement

VP designed the study and interpreted the data. VP and LG wrote the manuscript. MP, CS, TM, FCF collected the data and provided the literature search. All authors reviewed data and manuscript.

Declaration of competing interest

No conflict to declare.

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