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Venous thromboembolism and major bleeding in severe and critical COVID-19 hospitalized patients

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Abstract

Venous thromboembolism (VTE) and major bleeding (MB) are life-threatening complications described in COVID-19 hospitalized patients and they can be considered as two sides of the same coin. This retrospective study aims to evaluate the risk factors for VTE and MB in COVID-19 patients admitted to two Italian hospitals. The medical records of all COVID-19 patients (males 139; 62.3%, mean age 67.2±13.6 years, body weight 88.2±20.6 kg) hospitalized from March 11th to July 31st, 2020 to the Federico II University Hospital and to Sea Hospital, Naples, Italy, were analyzed. The COVID-19 patients were classified into four groups: COVID-19 patients developing VTE and/or MB, COVID-19 patients developing only VTE, COVID-19 patients developing only MB, and COVID-19 patients not developing neither VTE nor MB. During the hospitalization, 53 COVID-19 patients (24.7%; males 40; 75.5%, mean age 67.2±13.6 years, weight 88.2±20.6 kg) developed VTE, 33 COVID-19 patients (15.3 %; males 17; 51.5, mean age 67.3±14.9 years, weight 74.1±14.3 kg) developed MB, and 129 COVID-19 patients not developed neither TVP nor MB. No parameters to identify severe COVID-19 complicated by VTE and/or MB were found. However, some clinical and biochemical parameters can be evaluated to predict the risk of MB in order to modify the treatment and take prompt action to reduce mortality.

Key words: COVID-19; venous thromboembolism, spontaneous muscle hematoma.

Introduction

Since December 2019 the rapidly growing pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused more than 250 million infections worldwide and more than 5 million deaths [1,2]. The clinical features of coronavirus disease 19 (COVID-19) are variable and systemic, covering a large spectrum of illnesses ranging from asymptomatic infection to severe and critical diseases with clinical signs of respiratory and multiorgan failures, including coagulation abnormalities [3,4] with both hypercoagulability [venous thromboembolism (VTE)] and major bleeding (MB) complications (i.e., gastrointestinal bleeding, hemoptysis, oral bleeding, bleeding from multiple cannulation sites, intracranial hemorrhage, muscle hematomas, pulmonary and renal hemorrhages) [5-7]. In addition, the occurrence of VTE and MB together have been already described in other conditions that present with endothelial damage [8], as also observed in COVID-19 [9)]. So that, one can be considered as the reverse of the medal of the other.

Our recent metanalysis described an increased risk of VTE in patients with COVID-19, compared to patients with other viral pulmonary infections, such as influenza A [10]. This susceptibility is more evident in patients admitted to hospitals [10,11], and because of this they are usually managed with

prophylactic/therapeutic doses of low molecular weight heparin (LMWH). On the other hand, bleeding complications have also been reported in COVID-19 as much as in emergency setting as in stable patients, worsening the outcome and challenging the anticoagulant management [12,13].

Despite the reduced mortality and morbidity from COVID-19 (14), SARS-CoV2 still continues to represent a burden mostly in case of severe disease that needs hospitalization according to Italian criteria (https://www.agenas.gov.it/images/agenas/covid-19/Appropriatezza_setting_ospedalieri__COVID_2.0_17_6_2021.pdf). Given these premises, the prompt identification of risk factors for VTE or MB appears as a key point for effective and efficient management of hospitalized COVID-19 patients.

The study aims are to: i) describe the prevalence of VTE and MB; ii) identify the clinical and laboratory factors that contribute to the occurrence of both VTE and MB considered as a whole; iii) describe the differences between patients affected by VTE and by MB; iv) find out the risk factor for both or any in hospitalized COVID-19 patients. The study was performed in the Campania Region, Southern Italy, a region with a high incidence and prevalence of COVID-19 patients during the SARS-CoV-2 pandemic.

Material sand Methods

Patients

This retrospective study was performed by analyzing medical records of all COVID-19 patients referring from March 11th to July 31st, 2020, to the Federico II University of Naples and to the Sea Hospital of Naples, Italy. All data were obtained as part of administrative management and hospital care and the informed consent was signed from each patient involved in this study.

SARS-CoV-2 diagnostic tests

Diagnosis of SARS-CoV-2 infection was performed by nucleic acid amplification tests as real-time reverse-transcription polymerase chain reaction and, when necessary, it was confirmed by nucleic acid sequencing to identify the unique sequences of virus RNA, according to the World Health Organization criteria [15].

Italian criteria for hospitalization

According to criteria proposed by the Italian National Institute of Health, COVID-19 patients were in hospital admitted when they presented one or more of the following characteristics: a) moderate hypoxemia (arterial oxygen tension <60 mmHg or oxygen saturation <92% in ambient air) or a ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 or pulmonary infiltrates > 50%;

b) dyspnea at rest or for mild efforts (i.e. talking); c) oxygen saturation <90% during a walking test; d) a modified early warning score ≥ 5; e) changes in sensory state or other symptoms or signs of hypoperfusion and/or hypoxia (i.e., anuria, hypotension, acute coronary artery disease, cyanosis) (https://www.agenas.gov.it/images/agenas/covid-19/Appropriatezza_setting_ospedalieri__COVID_2.0_17_6_2021.pdf).

VTE and MB diagnosis

VTE consisted of symptomatic or incidental pulmonary embolism (PE), deep vein thrombosis (DVT) of the upper or lower extremities, cerebral sinus vein thrombosis or splanchnic vein thrombosis, confirmed by computed tomography (CT), magnetic resonance (MR) or ultrasound imaging [16,17]. The International Society on Thrombosis and Haemostasis (ISTH) definition of major bleeding was used, defining MB as 1) fatal bleeding, 2) symptomatic bleeding in a critical area or organ, or 3) bleeding causing a fall in hemoglobin level higher than 2 g/dL, or leading to a transfusion of 2 or more blood units [18].

Data form

A standardized, pre-piloted schedule was used to extract relevant clinical and laboratory data for this study. The extracted information is listed as follow: age; gender; body weight; history of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM); arterial hypertension; coronary heart disease; cancer; peripheral arterial disease (PAD), defined as all arterial diseases other than coronary arteries and the aorta, including the carotid and vertebral, the upper and lower extremities, mesenteric and renal arteries (26); cigarette smoking, ongoing pregnancy. Laboratory parameters at the admission evaluated for this analysis were: total blood count, estimated glomerular filtration rate (eGFR), D-dimer; C-reactive protein (CRP), procalcitonin (PCT), interleukin 6 (IL6), creatine kinase (CPK). Treatments at home, drugs administered during hospitalization (LWMH, antiplatelets agents, steroids), and death were recorded. Patients with incomplete data collection were excluded from the analysis. All data are available for consultation if requested.

Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics, version 27 (International Business Machines Corporation, Inc., Armonk, NY, USA). Analysis of variance (ANOVA) or chi-squared test and Fisher's exact test were used to assess differences between patients who developed and didn’t develop VTE, and between patients who developed and didn’t develop MB. Data are

expressed as means ±SD for continuous variables and as absolute, percentage values for discrete variables. A p-value <0.05 was considered statistically significant.

Results

Overall, in the lapse of time considered, 223 patients (males 139; 62.3%, mean age 67.2±13.6 years, body weight 88.2±20.6 kg) with severe and critical COVID-19 were admitted in the two Neapolitan Hospitals. During the hospitalization, 68 COVID-19 patients developed VTE (COVID-VTE) 5.6±1.4 days after the admission, 41 COVID-19 patients developed MB (COVID-MB) 12.7±2.3 days after the admission, and 114 COVID-19 patients did not develop neither VTE nor MB (COVID-C) and were considered as control. The clinical characteristic of patients affected by COVID-19 and VTE or MB considered in one group (COVID-VTE+MB) compared to COVID-C, COVID-MB and COVID-VTE are reported in Tables 1, 2 and 3.

COVID-VTE vs COVID-C

As reported in Table 3, COVID-VTE showed a lower PCT serum level compared to COVID-C. No additional significant differences between COVID-VTE and COVID-C were observed

COVID-MB vs COVID-C

At the time of the in-hospital admission, COVID-MB showed a higher prevalence of bacterial infection [OR 3.55 (1.61 - 7.85), p<0.01, Table 1] and of PAD [OR 2.24 (1.02 - 4.92), p<0.04, Table 2] compared to COVID-C. During the in hospital course, COVID-MB patients showed a significantly higher CPK serum levels compared to COVID-C, as reported in Table 3. COVID-MB patients presented also a higher risk of in-hospital death compared to COVID-C [OR 3.51 (1.59-7.73), p<0.01].

COVID-VTE vs COVID-MB

COVID-VTE patients showed a higher prevalence of men [OR 2.90 (1.15-7.31), p<0.04, Table 1], and obesity [OR 1.65 (1.07-2.54), p<0.01, Table 2] compared to COVID-MB. COVID-MB showed a higher prevalence of bacterial infection [OR 6.62 (2.48-17.63), p<0.01, Table 1] compared to COVID-VTE. COVID-MB patients showed a higher PCT and CPK serum levels compared to COVID-VTE, as reported in Table 3. COVID-MB patients presented a higher risk of in-hospital death compared to COVID-VTE [OR 3.44 (1.38-8.57), p<0.01].

Noteworthy, 2 COVID-patients (0.9%) showed both VTE and MB, with VTE preceding MB, in particular SMH. The first patient was a 58-year-old man and the other patient was a 73-year-old

woman, already described in a previous article by the same authors [20]. They were admitted to the Federico II Intensive Care Unit (ICU) because of the severe COVID-19, and both required non-invasive ventilation support. They developed VTE after 5 and 7 days from the admission respectively and were both treated with LWMH at a therapeutic dose. On the 7th and 10th day, respectively, SMH with hemodynamic instability occurred. The SMH interested the ileo-psoas muscle in the first patient, and the vastus intermedius muscle in the second patient. The patients were treated with arterial embolization guided by computed tomography (CT), blood transfusion and interruption of anticoagulant therapy. However, both patients died, on the 10th and 15th day after the admission, respectively.

Discussion

VTE and MB are two potentially lethal conditions that can complicate the clinical course of COVID-19 patients, in particular in case of hospitalization and can be considered as two features of the same condition [8,19]. This retrospective study was performed comparing the clinical and biochemical parameters of all consecutive COVID-19 patients admitted in two Italian Hospitals, classified according to the development of VTE (COVID-VTE), MB (COVID-MB), or neither (COVID-C) during the in-hospital course. The study results indicate that MB is the complication with the highest mortality risk, and that clinical and biochemical characteristics allow to draw a risk profile of patients admitted for COVID-19 into the hospital for the eventual occurrence of MB. COVID-MB presented indeed with bacterial infection and with higher PCT and CPK serum levels. In addition, two patients presented with both VTE and MB.

For the first time, the VTE and MB incidence was evaluated in the same study cohort. A plethora of clinical and experimental evidence demonstrated that the overproduction of early response proinflammatory cytokines)tumor necrosis factor, IL-6, and IL-1β), resulting in a “cytokine storm”, is the leading cause of the systemic complications reported in severe and critical COVID-19 diseases [20]. In particular, the cytokine storm significantly impacts the effects of COVID-19 on the vascular system, actively contributing to vascular damage, complement activation and coagulation activation [21]. In addition, the cytokine storm triggers the hemostasis system by increasing the fibrinolysis inhibitor from one side and tissue factor from the other [22]. These can lead to the reported episodes of VTE and of MB complications, that complicate the COVID-19 course. The occurrence of either VTE and/or MB was associated with excess mortality, underlying the importance of developing effective prevention and treatment strategies that reduce their frequency [23,24].

Katsoularis and colleagues described COVID-19 as an independent risk factor for VTE and MB [25], although failing in the determination of other co-factors that can interact with SARS-CoV2 infection

in the determination of either thrombotic or hemorrhagic complications. The clinical implication could be represented by the encouragement of a more precautionary approach in therapeutic management, making tip the balance one way or another.

The study has several strengths. We found that some clinical parameters and biomarkers are associated with the risk of MB in severe and critical COVID-19 hospitalized patients. They are quick to obtain in an emergency setting and affordable in any place. These parameters are already known to predict a poor outcome in COVID-19 patients, and so commonly evaluated at hospital admission. Given these premises, prompt identification of COVID-19 patients at increased risk of MB can be easier, to better manage the treatment in an emergency. Our study encompasses some limitations. The retrospective nature fails to define a causal connection and allows to describe just the association of the variables and it can be considered as a limitation.

In conclusion, even if MB and VTE share the same pathogenesis, our data didn't clarify a risk profile for patients affected by COVID-19 and complicated by any coagulopathy. However, MB is a complication of SARS-CoV2 infection that impact survival. Some clinical and biochemical parameters can be evaluated to predict the risk of such a condition, so as to tailor antithrombotic treatment to each fragile patient. Furthermore, the results of this study may be helpful also to acknowledge the clinical complications, that may affect subjects featured by a unique risk profile in case of viral infections resembling SARS-CoV2, such as influenza viruses [10].

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Table 1. Clinical characteristics of patients affected by SARS-CoV2 infection at the time of the hospitalization.

	COVID-VTE+MB	COVID-VTE	COVID-MB	COVID-C
Number (n; %)	86; 48.9	53; 24.7	33;15.3	129;60.0
Men (n; %)	57; 66.3	40; 75.5[b]	17; 51.5	82; 63.5
Women (n; %)	29; 33.7	13; 24.5[b]	16; 48.5	47; 36.4
Age (years)	67.9±14.0	67.2±13.6	67.3±14.9	67.8±13.2
Body weight (kg)	80.6±18.2	88.2±20.6[b]	74.1±14.3	84.0±21.9
LMWH (n; %)	46; 53.5	28; 52.8	18; 54.5	69; 53.5
Fondaparinux (n; %)	40; 46.5	25; 47.2	15; 45.5	60; 46.5
Antiplatelets (n; %)	24; 27.9	15; 28.3	9; 27.3	43; 33.3
Bacterial infection (n; %)	30; 34.9	10; 18.9[b]	20; 60.6[a]	39; 30.2
Mycotic infection (n; %)	6; 6.9	5; 9.4	1; 3.0	11; 8.5

The data are expressed as mean ± standard deviation for continuous variables and as absolute; percentage for discrete variables; COVID-VTE+MB: patients with COVID-19 and venous thrombo-embolism and/or major hemorrhage. COVID-VTE: patients with COVID-19 and venous thromboembolism. COVID-MB: patients with COVID-19 and major hemorrhage. COVID-C: control patients, with COVID-19, but without venous thrombo-embolism and/or major bleeding. LMWH: low molecular weight heparin. [a]statistically different when compared to controls. [b]statistically different when compared to patients with MB

Table 2. Comorbidities reported in patients affected by SARS-CoV-2 infection at the time of the hospitalization.

	COVID-VTE+MB	COVID-VTE	COVID-MB	COVID-C
Number	86	53	33	129
Hypertension (n; %)	53; 61.6	32; 60.4	21; 63.6	82; 63.6
T2DM (n; %)	26; 30.2	13; 24.5	13; 39.4	37; 28.7
Obesity (n; %)	51; 59.3	37; 69.8[b]	14; 42.8	32; 24.8
Neoplasm (n; %)	13; 15.1	7; 13.2	6; 18.2	15; 11.6
CAD (n; %)	22; 25.6	13; 24.5	9; 27.3	22; 17.1
PAD (n; %)	30; 34.9	15; 28.3	15; 45.5[a]	35; 27.1
CKD (n; %)	23; 26.7	12; 22.6	11; 33.3	44; 34.1
Smoking (n; %)	13; 15.1	7; 13.2	6; 18.2	26; 20.2

The data are expressed as absolute; percentage. COVID-VTE+MB: patients with COVID-19 and venous thrombo-embolism and/or major hemorrhage. COVID-VTE: patients with COVID-19 and venous thrombo-embolism. COVID-MB: patients with COVID-19 and major hemorrhage. COVID-C: control patients, with COVID-19, but without venous thrombo-embolism and/or major bleeding. T2DM: type 2 diabetes mellitus; Obesity: body mass index over 25 kg/m^2. Neoplasm: active neoplasm; CAD: Coronary artery disease; PAD: Peripheral artery disease; CKD: chronic Kidney disease, defined as estimated glomerular filtration rate < 30 $mL/min/1.73m^2$. Smoking: smoking habits; [a]statistically different when compared to Controls.

Table 3. Biochemical characteristics of patients affected by SARS-CoV2 infection at the time of the hospitalization.

	COVID-VTE+MB	COVID-VTE	COVID-MB	COVID-C
Hb (g/dl)	12.6±1.4	12.1±1.3	11.9±1.1	13.0±1.2
WBC (*10^3/µl)	12.1±5.5	13.2±7.5	10.7±4.2	11.7±5.4
Neutrophiles (*10^3/µl)	10.3±5.1	11.1±5.8	9.5±3.8	10.5±5.2
Lymphocytes (*10^3/µl)	1.4±3.3	1.6±4.6	0.7±0.5	2.3±4.1
Platelets (*10^3/µl)	264.2±125.7	268.5±130.9	244.1±121.9	262.5±111.1
CRP (mg/l)	47.9±72.7	39.7±75.2	61.6±62.0	46.5±72.4
PCT (ng/ml)	1.3±2.5	0.4±0.9 [a,b]	1.5±3.0	1.4±3.1
IL6 (pg/ml)	46.9±55.2	39.0±40.8	55.1±67.4	47.2±68.0
PT (sec)	14.4±5.9	14.3±7.4	13.8±3.8	14.4±5.9
PTT (sec)	28.1±3.9	27.2±4.5	27.8±3.4	29.0±4.3
Fibrinogen (g/dl)	637.6±222.1	617.9±203.8	581.3±214.8	658.5±222.6
D-dimer (mg/l)	4.4±3.2	3.6±3.4	2.9±3.5	5.5±3.5
Creatinine (md/dl)	2.9±1.1	1.9±2.3	1.3±1.0	3.0±1.1
Glucose (mg/dl)	134.5±82.0	187.4±102.4	173.1±74.5	134.6±71.0
AST (U/l)	49.6±75.1	42.9±25.4	79.2±256.7	44.2±51.2
LDH (U/l)	494.4±254.3	522.6±215.8	443.5±284.4	493.5±259.3
CPK (µg/l)	431.9±230.1	73.5±149.7[b]	2155.5±556.6[a]	136.6±149.7

The data are expressed as mean ± standard deviation; COVID-VTE+MB: patients with COVID-19 and venous thromboembolism and/or major hemorrhage. COVID-VTE: patients with COVID-19 and venous thromboembolism. COVID-MB: patients with COVID-19 and major hemorrhage. COVID-C: control patients, with COVID-19, but without venous thrombo-embolism and/or major bleeding. Hb: hemoglobin; WBC: white blood cell count; CRP: C-reactive protein; PCT: Procalcitonin; IL6: interleukin 6; PT: prothrombin time; PTT: partial thromboplastin time; LDH: lactic dehydrogenase; ASP: aspartate amino-transferase; CPK: creatine kinase. [a]statistically significant when compared to controls; [b]statistically significant when compared to patients with MB