Spontaneous Muscle Hematoma in Patients with COVID-19: A Systematic Literature Review with Description of an Additional Case Series

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Abstract

Coagulation abnormalities, thrombosis, and endothelial dysfunction have been described in COVID-19 patients. Spontaneous muscle hematoma (SMH) is a rare complication in COVID-19. The aims of this study are to: (1) perform a systematic review of the literature to better define the clinical SMH characteristics, (2) describe the prevalence and the clinical characteristics of SMH in COVID-19 patients referring to a Department of Internal Medicine (IM) (Federico II University of Naples), a Department of Sub-Intensive Care Medicine (SIM) (Ospedale Del Mare), and a Department of Intensive Care Unit (ICU) (Federico II University). The systematic review was performed according to PRISMA criteria. The local prevalence of SMH in COVID-19 was evaluated retrospectively. The medical records of all COVID-19 patients referring to IM and ICU from March 11th, 2020, to February 28th, 2021 were examined for SMH occurrence. In our retrospective analysis, we describe 10 cases of COVID-19 patients with SMH not previously reported in literature, with a prevalence of 2.1%. The literature review, inclusive of our case series, describes a total of 50 SMHs in COVID-19 patients (57.4% males; mean age 68.8 ± 10.0 years). The SMH sites were ileo-psoas, vastus intermedius, gluteus, sternocleidomastoid, and pectoralis major muscles. Males developed SMH earlier than females (9.5 ± 7.8 vs. 17.1 ± 9.7 days). Ileo-psoas hematoma was more frequent in males (69.2 vs. 30.8%), while pectoralis major hematoma occurred only in females. The in-hospital mortality rate of SMH in COVID-19 patients was 32.4%. SMH is a rare but severe complication in COVID-19 hospitalized patients, associated with high mortality. A gender difference seems to be present in the clinical presentation of the disorder.

Keywords
- muscle hematoma
- COVID-19
- SARS-CoV-2
- ileo-psoas

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Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Its clinical protean features range from asymptomatic or pauci-symptomatic disease, mostly managed at home, to a systemic disease with pneumonia and extra pulmonary involvement, which can lead to hospitalization in intensive care unit (ICU).[1–3]

Risk factors for a more severe COVID-19 clinical expressiveness are male gender, elderly age, arterial hypertension, obesity, diabetes mellitus, cardiovascular and renal diseases, among others.[4]

Coagulation abnormalities, thrombosis, and endothelial dysfunction are often seen in COVID-19, with higher incidence in severe cases and especially in ICU patients.[4] The severity of alterations of coagulation parameters (mainly high D-dimer, prolonged prothrombin time (PT), and thrombocytopenia) has been clearly associated with unfavorable prognosis.[5–8] Indeed, severe COVID-19 possibly represents a peculiar form of viral sepsis, and the pathogenesis of the COVID-19 induced coagulopathy may overlap with that of bacteria-induced septic coagulopathy or disseminated intravascular coagulation (DIC), but with prominent pro-thrombotic feature.[1] Both arterial (myocardial infarction and ischemic stroke) and venous thromboses (pulmonary embolism and deep venous thrombosis) are frequent in patients with severe COVID-19, though in situ pulmonary thrombosis is also commonplace and cases of DIC have also been described.[5] According to recent statements and guidelines, all hospitalized patients with COVID-19 should receive some forms of pharmacological thromboprophylaxis, unless there are specific contraindications, even if evidence regarding the most appropriate prophylactic anticoagulant and regimen are still being gathered.[9–14] Bleeding tendency in COVID-19 is uncommon, but has been described as possible consequence of imbalances in platelet production/disruption, coagulation disorders, and antithrombotic prophylaxis.[15–17] Nevertheless, in addition to thrombotic complications, bleeding may represent a significant cause of morbidity and mortality in COVID-19.[17] Types of bleeding may include gastrointestinal bleeding, hemoptysis, oral mucosa bleeding, bleeding from multiple cannulation sites, intracranial hemorrhage, internal bleeding, pulmonary and renal hemorrhages.[17] Spontaneous muscle hematoma (SMH) is a rare complication in COVID-19 patients[18] and its clinical characteristics have not yet been fully described.

In this hybrid article, we describe the findings of a systematic review to better describe the clinical characteristics of SMH in COVID-19. The findings of this systematic review were supplemented with the clinical characteristics of patients with COVID-19 complicated by SMH referred to the Department of Internal Medicine (IM) and the Department of ICU of Federico II University (Naples, Italy), and to the Department of Sub-Intensive Care Medicine (SIM) of the Ospedale Del Mare (Naples, Italy).

Methods

Retrospective Local Study

The retrospective study was performed analyzing the medical records of all COVID-19 patients referring from March 11th, 2020, to February 28th, 2021, at IM, SIM, and ICU.

On their first admission, all patients were informed that (1) their personal data, collected as part of administrative management and hospital care, could be used for health research purposes, under the responsibility of the Federico II University of Naples and the Ospedale Del Mare of Naples; (2) they could withdraw their consent to the use of personal data without providing further explanation at any time and without medical assistance being affected. This, in the form of written informed consent, was obtained from each patient or subject involved in this study. According to WHO,[19] detection of unique sequences of virus RNA was obtained by Nucleic acid amplification tests such as real-time reverse-transcription polymerase chain reaction (rRT-PCR) with confirmation by nucleic acid sequencing, when necessary, to confirm the SARS-CoV-2 infection.

The SMH was diagnosed based on computed tomography (CT) appearance: acute bleeds appear as focal areas of high attenuation that, over time, demonstrate decreasing attenuation due to clot lysis. In addition, diffuse parenchymal hemorrhage may present solely as isodense enlargement of the involved muscle.[20]

Systematic Review

A systematic search of the medical literature was also performed in Google Scholar, Google book, and Medline (last conducted search April 3rd, 2021) using the following terms: "muscle hematoma," "COVID-19," and "ileo-psoas hematoma." There were no language restrictions.

Study Selection

Eligible studies were case reports, case series, and review articles. Predetermined inclusion criteria were patients of all ages with occurrence of muscle hematoma during SARS-CoV-2 infection. Exclusion criteria were patients with genetic bleeding disorders, such as hemophilia, von Willebrand disease, and patients with liver cirrhosis. Titles and abstracts (when available) of studies retrieved using the search strategy were screened independently by two review authors (V.A., A.C.) to identify studies that potentially met the inclusion criteria outlined above. The full text of potentially eligible studies was retrieved and independently assessed for eligibility by the two review team members. Studies in language different from English, French, and Italian were translated in English or Italian by a specialist translator. Any disagreement over the eligibility of studies was resolved through discussion with a third and a fourth reviewer (D.R., A.T.). The reference lists of all identified articles were searched for further relevant publications.

Data Form

A standardized, pre-piloted form was used to extract relevant clinical data from the included studies. The extracted information included: age, gender, comorbidities (such as diabetes mellitus, arterial hypertension, chronic ischemic heart disease, cancers), body weight; blood pressure, hemoglobin, lymphocytes, platelets, glomerular filtration rate, PT, international normalized ratio (INR), activated partial thromboplastin time (aPTT), D-dimer, fibrinogen, ferritin, C-reactive protein (before and after the occurrence of hematoma); treatment with low-

weight molecular heparin (LWMH), antiplatelets agents, hydroxychloroquine, steroids, antiviral agents, oxygen, noninvasive ventilation; days from the onset of symptoms to hospitalization; days of hospitalization; days of treatment with LWMH; eventual treatment of the hematoma; mobilization during the hospitalization; exitus.

Statistical Analysis

Statistical analysis was performed using an IBM SPSS (Statistical Package for Social Science), version 25 (IBM, Armonk, NY). The data were expressed as mean ± standard deviation and absolute values; percentage number for continuous and categorical variables, respectively. In each table was also reported the absolute number of subjects in whom each clinical and biochemical parameter was available. In univariate analysis, statistical comparisons were based on Student's *t*-test, with Bonferroni correction when required, for continuous variables and on Chi-square test for dichotomous variables. Logistic regression models, based on the results of univariate analysis, were generated to evaluate the possible statistical interference between the given variables. All statistical tests were two-tailed. A p-value <0.05 was considered significant.

Results

Retrospective Study

The retrospective study identified 10 patients with COVID-19 complicated by SMH referring to IM, ICU, and SIM. In the same timeframe, 475 COVID-19 patients were referred to IM, ICU, and SIM, so that the overall prevalence of local SMH was 2.1%.

Five patients (50%) were males and five (50%) were females. Mean age was 63.5 ± 9.0 years. The patients were admitted 5.3 ± 7.0 days after the first COVID-19 symptoms, because of occurrence of acute lung dysfunction. At admission, three patients (30%) continued aspirin long-term treatment, all patients (100%) were treated with high dose steroids, four patients (40%) received LWMH at prophylactic dose (4,000 UI if the body weight was <80 kg, or 6,000 UI if the body weight was ≥80 kg), six patients (60%) at therapeutic dose (100 UI/kg twice daily). Seven patients (70%) were treated with noninvasive ventilation. All patients had been mobilized during the in-hospital stay, because of the need for pronation and physiotherapy.

SMHs were diagnosed 15.1 ± 9.9 days after the start of the therapy with LWMH. In five cases the hematomas appeared in ileo-psoas muscle (►**Figs. 1** and **2**), in three cases in the vastus intermedius muscle, in one case in the large pectoral and in another one in the gluteus. As comorbidities are concerned, six (60%) of our patients had type-2 diabetes mellitus, five (50%) arterial hypertension, and three (30%) coronary artery disease. All but two patients (80%) had cough as main symptom of SARS-CoV-2 infection.

Six patients (male 3, 50%; female 3, 50%; mean age 65.8 ± 6.4 years) received radiological embolization (►**Figs. 3** and **4**) whereas the remaining four patients (male 2, 50%; female 2, 50%; mean age 60.0 ± 12.1 years) received conservative treatment, with blood transfusion.

Systematic Review

As reported in ►**Fig. 5**, performed according to PRISMA criteria,[21] 17 studies were included in qualitative and quantitative syntheses.[16,22–37] The systematic review identified 40 patients with COVID-19 complicated by muscular hematomas.

Therefore, the final number of COVID-19 patients evaluated, including those ($n = 10$) in our case series, was 50. Clinical and biochemical parameters at hospitalization of COVID-19 patients with SMH, classified for gender, are summarized in ►**Table 1**, where data was available. Of interest, 10 male COVID-19 patients with SMH were affected by coronary artery disease as comorbidity. During hospitalization, 20/45 (44.4%) received LMWH at prophylactic dose and 25/45 (55.6%) at therapeutic dose. In the remaining five cases the information was not available.

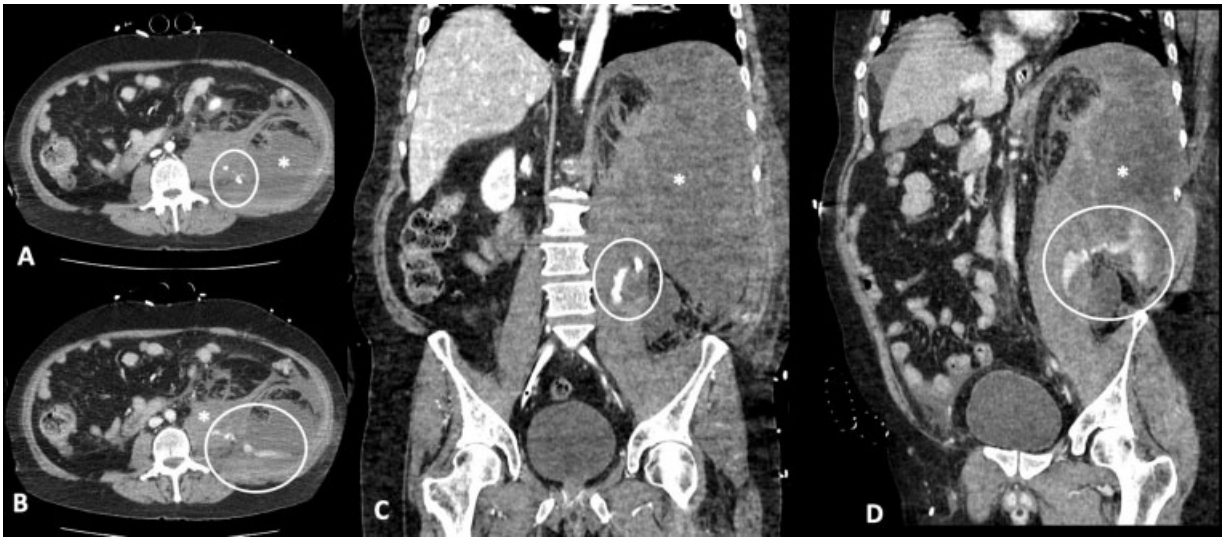

Fig. 1 Extensive retroperitoneal hematoma (*asterisk*) with active bleeding (*white circle*) detected by MultiDetector computed tomography axial scan (**A, B**) with coronal (**C**) and oblique coronal (**D**) multiplanar reconstruction.

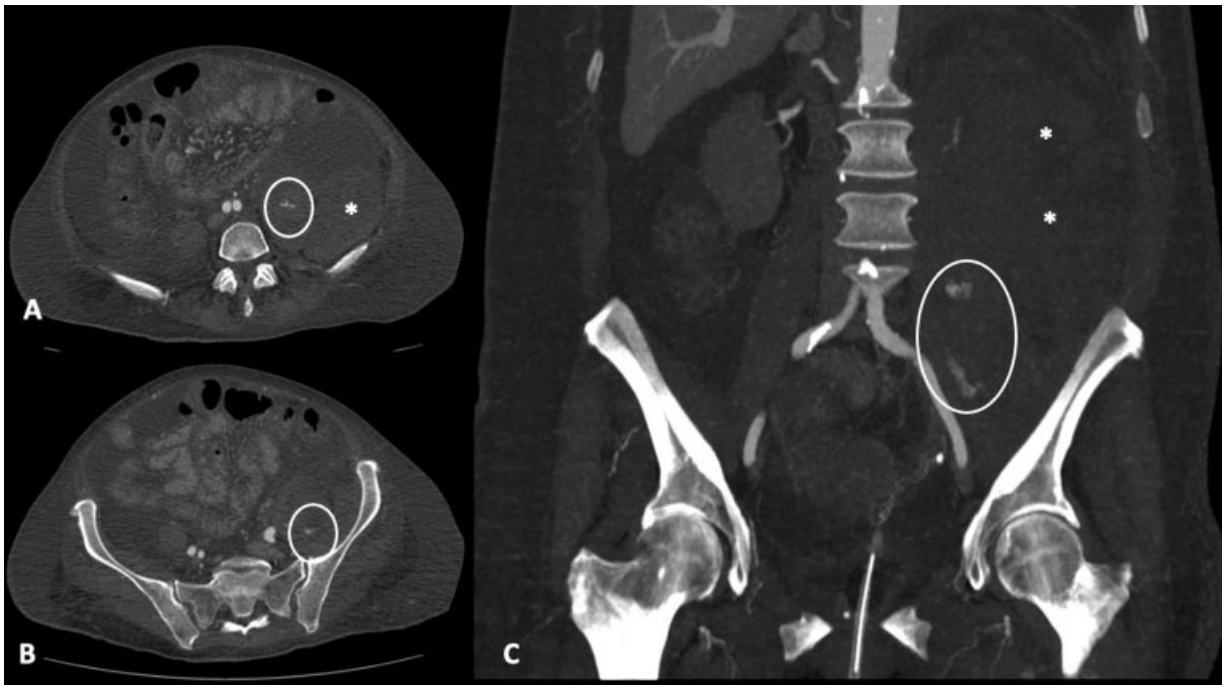

Fig. 2 Extensive retroperitoneal hematoma (*asterisk*) with active bleeding (*white circle*) detected by MultiDetector computed tomography axial scan (**A, B**) with coronal (**C**) multiplanar reconstruction.

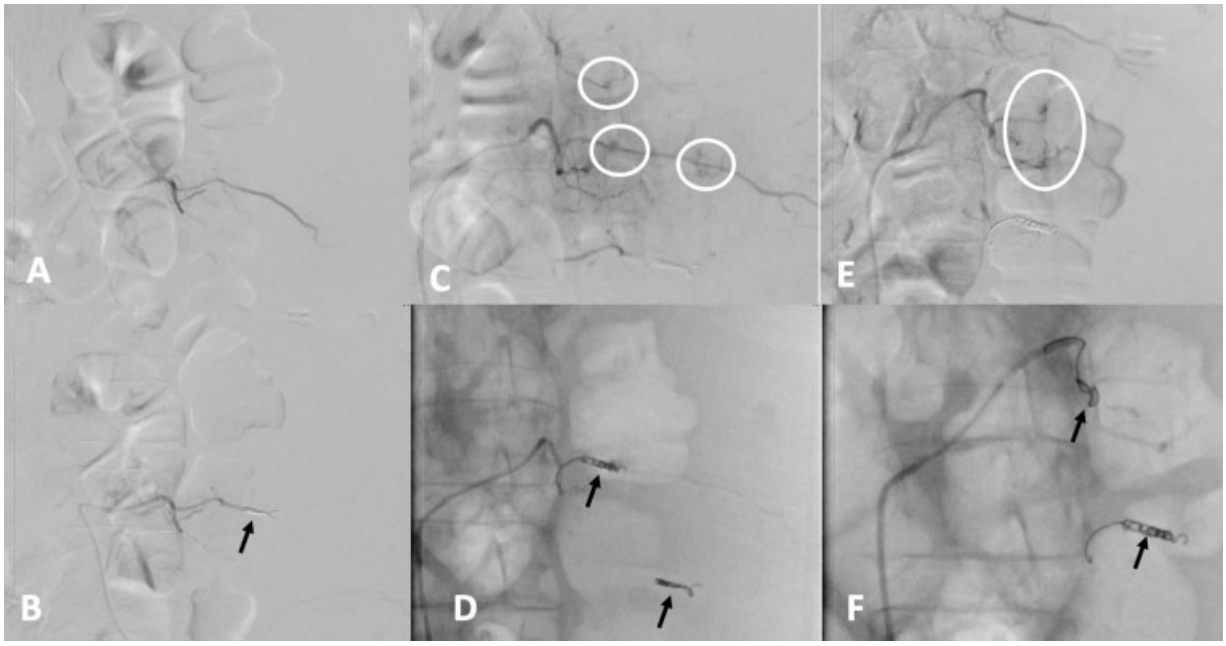

Fig. 3 Angiography showing the second, third, and fourth left lumbar arteries before (**A**, **C**, and **E**, respectively) and after (**B**, **D**, and **F**, respectively) embolization. Therapeutic procedure was performed in the patient depicted in ►**Fig. 2.** Black arrows, endovascular embolization; White circle, active hemorrhage.

The SMH appeared 14.2 ± 9.3 days after start of treatment with LWMH. Interestingly, males developed SMH earlier than females (9.6 ± 8.3 vs. 17.7 ± 10.2, days for males and females respectively; $p = 0.03$). This result remains significant also after correction for age, comorbidities reported in ►**Table 1** and LWMH doses (therapeutic vs. prophylactic doses).

The exact localization of SMH was known in 40 COVID-19 patients. As reported in ►**Table 2**, where data was available, the overall distribution of SMH was significantly different between males and females. In effect, despite the most frequent localization of SMH being ileo-psoas muscle in both genders, this complication occurred preferentially in males compared with females. On the contrary, the occurrence of SMH in pectoralis major was higher in females compared with males. Of interest, all patients developing SMH in prophylactic LMWH dose had preferential ileo-psoas localization.

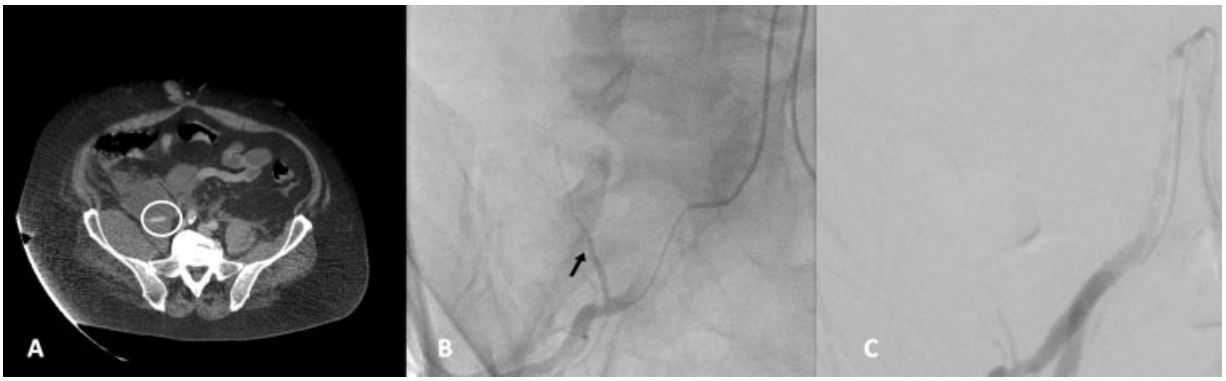

Fig. 4 Multidetector computed tomography axial scan (**A**) and angiography before (**B**) and after (**C**) embolization of the right ileo-lumbar artery. White circle: active hemorrhage. Black arrow: catheter for endovascular embolization.

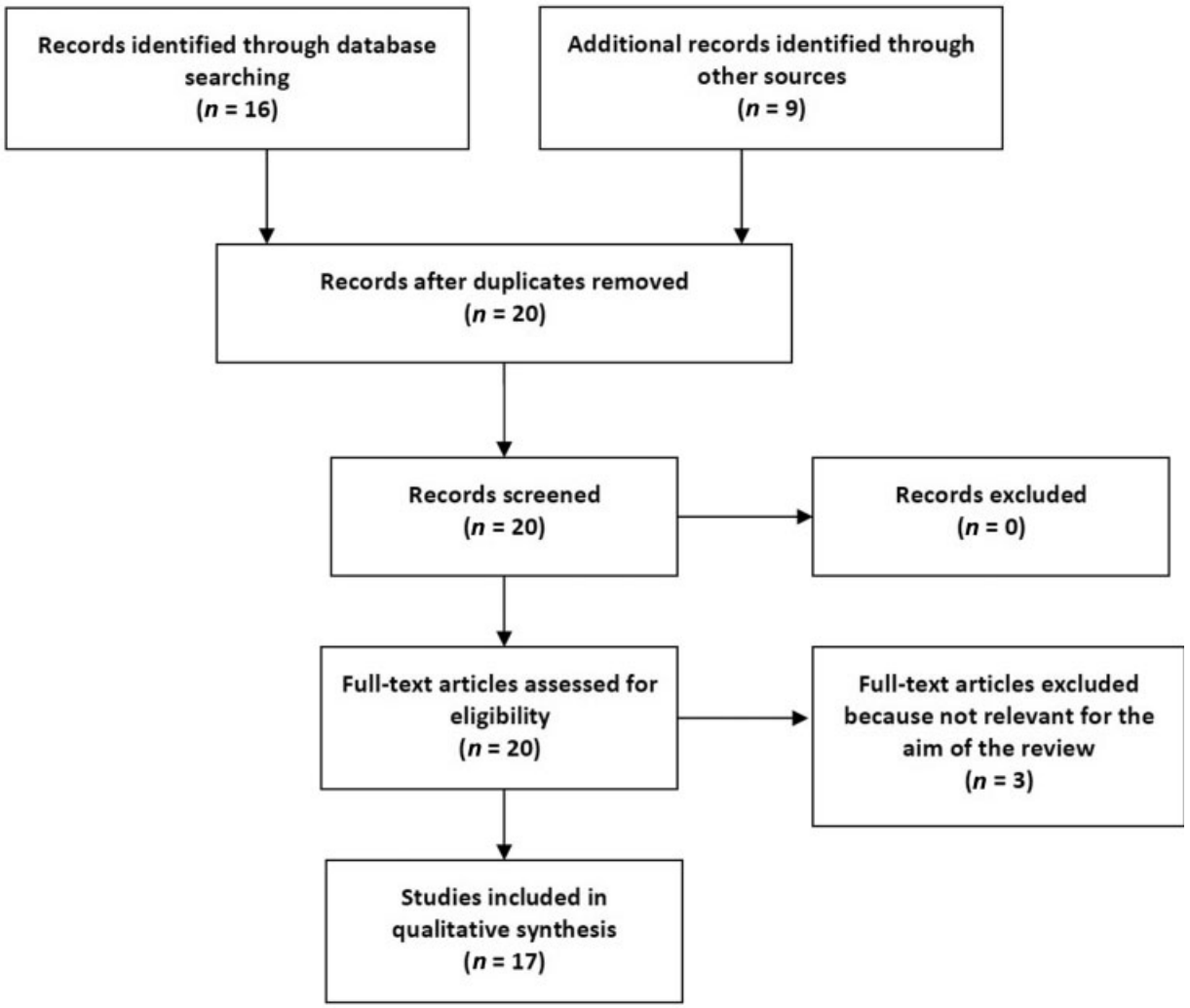

Fig. 5 PRISMA study flowchart.

The data regarding the therapeutic management was available for 28 COVID-19 patients. Of them, 17 patients (male 11, 64.7%; female 6, 35.3%; mean age 70.1 ± 7.7 years) received radiological embolization and 11 patients (male 4, 36.4%; female 7, 63.6%; mean age 60.0 ± 12.1 years) received conservative treatment.

The overall in-hospital mortality rate was 32.4% (11/34, available data). Clinical and biochemical characteristics of COVID-19 patients with SMH, classified according to clinical outcome, are shown in ►**Table 3**. No significant differences could be identified between SMH COVID-19 patients dead and those alive.

Table 1 Clinical and biochemical characteristics of COVID-19 patients with spontaneous muscle hematoma at hospitalization

	N	Males	Females	*p*-Value
Patients	47	27	20	
Age (years)	46	68.2 ± 8.2	68.9 ± 10.5	0.39
T2DM (*n*; %)	31	10; 58.8	4; 28.6	0.15
Hypertension (*n*; %)	31	12; 70.6	9; 64.3	0.99
Neoplasm (*n*; %)	31	1; 5.9	0; 0	0.99
CAD (*n*; %)	32	10; 55.6	2; 14.3	0.03
eGFR (-mL/min/1.73 m^2)	13	71.4 ± 34.3	72.7 ± 39.8	0.95
Hb (g/L)	26	128 ± 21	121 ± 13	0.32
Platelets (10^9/L)	28	211 ± 61	234 ± 70	0.37
Lymphocytes (10^9/L)	18	0.6 ± 0.3	1.1 ± 1.5	0.29
LDH (U/L)	13	288 ± 69	517 ± 391	0.19
D-dimer (mg/L)	29	2.0 ± 2.5	7.4 ± 14.7	0.16
Fibrinogen (g/L)	24	5.6 ± 2.0	6.9 ± 3.0	0.23
Ferritin (nmol/L)	14	1.8 ± 1.4	2.4 ± 3.7	0.68
INR	18	1.2 ± 0.2	1.2 ± 0.2	0.87
aPTT (ratio)	10	0.9 ± 0.3	0.9 ± 0.2	0.95
C-reactive protein (mg/L)	22	33.9 ± 39.0	24.9 ± 23.2	0.55

Abbreviations: aPTT, activated partial thromboplastin time; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Hypertension, arterial hypertension; INR, international normalized ratio; LDH: lactic dehydrogenase; *N*, absolute number of subjects in whom each clinical and biochemical parameter was available; T2DM, diabetes mellitus type-2.

Note: The data represent that available (i.e., some missing data) and are expressed as mean ± standard deviation or absolute; percentage number for continuous and categorical variables, respectively; $p = p$-values were based on Student's *t*-test, with Bonferroni correction when required, for continuous variables and on Chi-square test for dichotomous variables.

Table 2 The overall distribution of spontaneous muscle hematoma between COVID-19 male and female patients

	Male	Female	*p*-Value
Ileo-psoas muscle (*n*; %)	20; 83.3	9; 56.3	0.02
Vastus intermedius muscle (*n*; %)	1; 4.2	3; 18.8	
Gluteus muscle (*n*; %)	2; 8.3	0; 0.0	
Sternocleidomastoid muscle (*n*; %)	1; 4.2	0; 0.0	
Pectoralis major muscle (*n*; %)	0; 0.0	4; 25.0	

Abbreviation: COVID-19, coronavirus disease 2019.

Note: The data represent that available (i.e., some missing data) and are expressed as absolute and percentage; *p*-values have been calculated with Chi-square test.

Discussion

SMHs are a common and serious complication of congenital (hemophilia) or acquired coagulation disorders, and anticoagulant treatment. Among COVID-19 patients with SMH evaluated in our study, just two were affected by acquired hemophilia.[34,35] All other showed normal aPTT, essentially excluding hemophilia from the etiology of the SMH.[38] In addition, other laboratory tests, including platelets, INR, fibrinogen, and the fibrinolysis marker D-dimer were found to be normal, thereby highly excluding DIC.[39] Outside of COVID-19, the incidence of SMH in patients on anticoagulants is 0.6%, with higher prevalence in the elderly.[40] Our study demonstrated that SMH can be considered a rare but not negligible complication of COVID-19 in subjects with severe illness requiring in-hospital admission. Indeed, SMH was present in 2.1% of COVID-19 local patients. The study results also demonstrated that the occurrence of SMH significantly impact the prognosis of COVID-19 patients, since in-hospital mortality in this setting was as high as 32.4%.

Different pathogenic mechanisms could be taken in account to explain the increased susceptibility of SMH in COVID-19 patients. Endothelial injury may be due to the direct infection by SARS-CoV-2, inducing intracellular oxidative stress, and/or to profound systemic inflammatory response. Considering the potential association of COVID-19 with endothelial injury, it seems plausible that patients with preexisting endothelial dysfunction may be more vulnerable to severe disease course given the role of endothelial cells in vascular homeostasis.[41] We hypothesize that the endothelial dysfunction, in addition to administration of LWMH, may promote bleeding. This pathogenic link has been demonstrated in other infections.[42] On the other hand, treatment with dexamethasone in COVID-19 patients may inhibit platelet aggregation, concurring to SMH occurrence.[43]

In our study, the SMH in COVID-19 patients was found to have different distribution between males and females. In particular, we observed higher prevalence of ileo-psoas SMH in males compared with females. On the other hand, a higher prevalence of pectoralis major SMH was identified in females. These results are suggestive of a sexual dimorphism in the clinical presentation of SMH, which could be explained by anatomical differences in the muscle structure between sexes. As previously demonstrated, trunk and hip flexor strength of psoas increases proportionately with increases in lumbar lordosis, and females tend to have more exaggerated lordosis than males. Furthermore, females are usually shorter, with relatively wider pelvises such that their psoas

Table 3 Clinical and biochemical characteristics of COVID-19 patients with spontaneous muscle hematoma classified for outcome

	N	Dead	Alive	*p*-Value
Patients (*n*; %)	34	11; 32.4	23; 67.6	
M:F (*n*; %)	31	5; 55.6: 4; 44.4	11; 50.0: 11; 50.0	0.99
Age (years)	31	67.9 ± 8.34	70.0 ± 12.1	0.64
T2DM (*n*; %)	25	5; 62.5	8; 47.1	0.67
Hypertension (*n*; %)	25	4; 50.0	13; 76.5	0.36
Neoplasm (*n*; %)	25	0; 0	0; 0	
CAD (*n*; %)	26	2; 22.2	9; 52.9	0.22
eGFR (mL/min/1.73 m^2)	13	74.4 ± 42.2	70.5 ± 33.4	0.85
Hb (g/L)	21	131 ± 15	123 ± 20	0.41
Platelets (10^9/L)	25	242.7 ± 83.8	217.7 ± 61.9	0.42
Lymphocytes (10^9/L)	17	0.5 ± 0.1	0.5 ± 0.4	0.98
LDH (U/L)	12	309.2 ± 58.6	347.4 ± 129.5	0.56
D-dimer (mg/L)	29	1.4 ± 0.6	3.3 ± 5.0	0.24
Fibrinogen (g/L)	22	6.0 ± 2.1	5.8 ± 2.1	0.83
Ferritin (nmol/L)	12	3.3 ± 2.3	2.1 ± 3.1	0.63
INR	17	1.2 ± 0.2	1.1 ± 0.1	0.50
aPTT (ratio)	9	1.1 ± 0.3	0.8 ± 0.1	0.09
C-reactive protein (mg/L)	20	27.4 ± 15.6	29.9 ± 40.6	0.89

Abbreviations: aPTT, activated partial thromboplastin time; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; Dead, patients who died for any cause during the hospitalization; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Hypertension, arterial hypertension; INR, international normalized ratio; LDH, lactic dehydrogenase; *N°*, absolute number of subjects in whom each clinical and biochemical parameter was available; Alive, patients who survived and have been discharged; T2DM, diabetes mellitus type-2.
Note: The data represent that available (i.e., some missing data) and are expressed as mean ± standard deviation or absolute; percentage number for continuous and categorical variables, respectively; $p = p$-Values were based on Student's *t*-test, with Bonferroni correction when required, for continuous variables and on Chi-square test for dichotomous variables.

insertion angles may be less acute than in males. These potential mechanical advantages may mean that comparatively less psoas muscle bulk is required in females than in males to generate a given force.[44] This may be the reason for the higher prevalence of ileo-psoas hematoma in males than females.

Regarding pectoral hematoma, Bartolomei et al indicated that male individuals had significantly higher values of bulk and strength in trapezius, pectoral, and vastus lateralis muscles, compared with females.[45]

In addition, males displayed earlier onset of SMH compared with female. This can be framed in the contest of a more severe clinical expressiveness of COVID-19 in males observed in China and in other Countries, such as Italy.[46] This difference may be due both to hormonal differences and comorbidities. In males, the androgen receptor activates the transcription of a transmembrane protease serine 2, the activity of which appears key to SARS-CoV-2 virus spread and aggressiveness in the infected hosts, through the priming of viral spike protein. On the other hand, comorbidities have been reported as important clinical predictors in COVID-19 infection, and a sexually dimorphic phenotypic expression of the main underlying disease, such as coronary artery disease,[47] could possibly have a role in explaining the different outcomes between genders.[46,48] Aside from biological factors, gender-based behavioral and lifestyle differences may contribute to the male predisposition for more severe disease. Smoking is a well-known predisposition factor for cardiopulmonary comorbidities through alteration of the renin-angiotensin-aldosterone system homeostasis.[46]

Based on clinical evaluation, therapeutic options available for SMH are supportive care and blood transfusion alone, embolization procedures and surgical procedures.[49] In the systematic review including our patients,17 COVID-19 patients with SMH were identified for radiological treatment without influencing prognosis.

The combination of SARS-CoV-2 infection and SMH was associated with higher risk of death, calculated to be 32.4%, according to our findings. Outside of SARS-CoV-2 infection, the overall mortality rate calculated for SMH is of 4.5%.[40] In this regard, the COVID-19 may have contributed to increase the risk of unfavorable outcome, as the mortality rate in COVID-19 ICU in Italy has been reported to be as high as 27%.[50]

Conclusion

COVID-19 may be considered a risk factor for SMH, acting either directly (i.e., through endothelial injury) or indirectly (i.e., for the need of establishing anticoagulant treatment). In

particular, the prevalence seems to be higher in males, who develop more frequently SMH in ileo-psoas muscle and with earlier onset. The mortality rate seems also to be enhanced in patients with combination of COVID-19 and SMH.

Conflict of Interest
None declared.

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