

Analysis of Risk Factors of Soft Tissue Bleeding in COVID-19 Patients: A Point of View After Two Years of Pandemic

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Abstract

Background: The aim of the study was to analyze the relationship between patient characteristics, including anagraphic and laboratoristic data and amount of adipose tissue measured in computed tomography (CT) scans in coronavirus disease 2019 (COVID-19) patients, and incidence of soft tissue bleeding requiring medical and/or interventional radiology management.

Methods: A total of 132 patients hospitalized for COVID-19 pathology from October 2020 to May 2021 were included in the study and divided into two groups: a bleeding group of 70 cases with soft tissue bleeding occurring during hospitalization, and a control group of 62 hospitalized COVID-19 patients without bleeding events. In the bleeding group, two subgroups were considered: an embolization group including soft tissue bleeding cases requiring interventional radiology with transarterial embolization (TAE) (16/70; 22.9%) and a non-embolization group, clinically managed without TAE (54/70; 77.1%). Demographics and clinical data, visceral adipose tissue (VAT) area and subcutaneous adipose tissue (SAT) area measured on CT images and VAT/SAT ratio were compared between bleeding and control groups and between embolization and non-embolization subgroups.

Results: Bleeding and control groups did not significantly differ for sex distribution, COVID-19, platelet (PLT) count, international normalized ratio (INR), SAT area, VAT area, and VAT/SAT ratio. Embolization and non-embolization groups did not significantly differ for age, COVID-19, PLT count, INR, SAT area, and VAT/SAT ratio.

Bleeding group had lower body mass index (BMI) than control group as well as embolization group compared to non-embolization group. A statistically significant difference was observed between embolization and non-embolization groups for VAT area, with smaller values in embolization group (mean difference: 64.2 cm², 95% confidence interval: 8.3 - 120.1; $P < 0.05$).

Conclusion: Soft tissue bleeding in COVID-19 is more frequent and severe in patients with low amount of VAT, demonstrating that fat mass may have a containing function on bleeding, limiting its progression in surrounding structures. There are some other factors that influence the risk of bleeding, such as age, thromboprophylaxis therapy and BMI.

Keywords: SARS-CoV-2 infection; Visceral fat; Soft tissue bleeding; Embolization

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO) for its huge impact on health systems [1]. Respiratory system involvement is considered the principal cause of death in patients with COVID-19 [2, 3], although changes in coagulation function have been also commonly associated with SARS-CoV-2 infection as one of the most important adverse prognostic signs [4, 5]. Dysregulation of coagulation caused by host response to viral replication produces a hypercoagulability state often resulting in venous and arterial thrombosis and multiorgan dysfunction [6]. Consequently, heparin-based therapies were introduced [7] which, together with factors such as thrombocytopenia, hyperfibrinolytic state and consumption of coagulation factors, produce a higher risk of bleedings [8-10] in patients affected by COVID-19, including soft tissue hematomas requiring medical or interventional radiology management through transarterial embolization (TAE) [11]. Several studies showed a strong association between obesity and COVID-19 severity [12-17]. Obese patients affected by COVID-19 demonstrated an overall worse disease

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outcome with more severe infection forms, higher hospitalization and mechanical ventilation rates [18] compared to non-obese subjects. COVID-19 coagulopathy is also aggravated by obesity due to its intrinsic coagulation alterations that are in addition to those with those related to the SARS-CoV-2 infection [19]. In particular, excess visceral fat is considered an important risk factor for COVID-19 severity due to its viral receptor and cytokine expression [20]. The aim of this study was to analyze the relationship between patient characteristics, including anagraphic data and laboratoristic data and the amount of adipose tissue measured in computed tomography (CT) scans in COVID-19 patients, and the incidence of soft tissue bleeding requiring medical and/or interventional radiology management.

Materials and Methods

Ethical review and approval were waived for this study, due to retrospective nature of the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Study population

Patients admitted to our institution with more than 18 years of age and patients who were tested positive to COVID-19 were included. Patients admitted to our institution with less than 18 years of age or patients who were tested negative to COVID-19 were excluded.

A total of 132 patients hospitalized at our center for COVID-19 pathology from October 2020 to May 2021 were included in the study and divided into two groups: a bleeding group, including 70 cases of soft tissue bleeding occurring during hospitalization, and a control group, with 62 hospitalized COVID-19 patients without bleeding events. In the bleeding group, two subgroups were considered: an embolization group including soft tissue bleeding cases which required interventional radiology treatment with TAE (16/70; 22.9%) and a non-embolization group of soft tissue bleeding cases which were clinically managed without TAE (54/70; 77.1%).

Soft tissue bleeding management

In cases of soft tissue bleeding, conservative management was the main strategy for hemodynamically stable patients. TAE was performed in cases of progressive, uncontrolled bleeding (confirmed by CT angiography) leading to hemodynamic instability. Embolizing techniques included coils alone, glue alone, gelfoam alone and combinations of microparticles with coils, gelfoam and coils, and glue and coils (Figs. 1 and 2). Bleeding sites and embolization techniques are listed in Table 1.

Data collection

Demographics and clinical data were collected including body mass index (BMI), platelet (PLT) count, international normalized ratio (INR) and hemoglobin levels (Hb) at the patient admission and pulmonary involvement severity score (SS) [21, 22]. We also counted how many days after admission bleeding occurred, estimating the time of admission to the hospital with the start of anticoagulant therapy. At least one CT examination was performed in all patients during hospitalization, with contrast medium administration, using a dual source 384-slice (2×192) CT (Siemens SOMATOM Force, Erlangen, Germany) with real-time voltage modulation (70 - 150 kV), real-time dose modulation (CARE Dose4D™; 80 - 250 mAs), spiral pitch factor of 1.8 and collimation width of 0.6 mm. Measurements of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) areas in cm^2 were obtained by analyzing axial CT images at the level of the third lumbar vertebra with an image processing application (OsiriX, Pixmeo, Bernex, Switzerland) (Fig. 3) [23].

Statistical analysis

Demographics and clinical data, VAT and SAT areas and the VAT/SAT ratio were compared between the bleeding and the control groups using Chi-square and Student's *t*-test. The same variables were then compared between the embolization and non-embolization subgroups using Chi-square and Student's *t*-test.

To explore the risk factors associated with bleeding event and with TAE procedure, a multivariate logistic regression analysis was conducted. The following continuous variables were included in the analysis: sex, age, BMI, PLT, INR and Hb.

Statistical significance was considered as $P < 0.05$. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA).

Results

The bleeding group consisted of 70 cases while the control group included 62 cases. Bleeding never occurred before 4 days after admission, with a mean of onset of 8 days. All patient received heparin therapy for thromboprophylaxis during hospitalization and none had known pre-existing coagulation disorders. Bleeding and control groups did not significantly differ for sex distribution, COVID-19 SS, PLT count, INR, SAT area, VAT area and VAT/SAT ratio, although SAT and VAT areas tend to be lower in the bleeding group, although in a non-significant way. There was a slightly significant difference in age between bleeding group and control group, with older patients in the former and a mean difference of 6 years (95% confidence interval (CI): 0.4 - 11.6; $P < 0.05$). There was a slight significant difference in BMI between bleeding group and control group, with lower values in the former.

The embolization group consisted of 16 cases, while the non-embolization group included 54 cases. Embolization and non-embolization groups did not significantly differ for age,

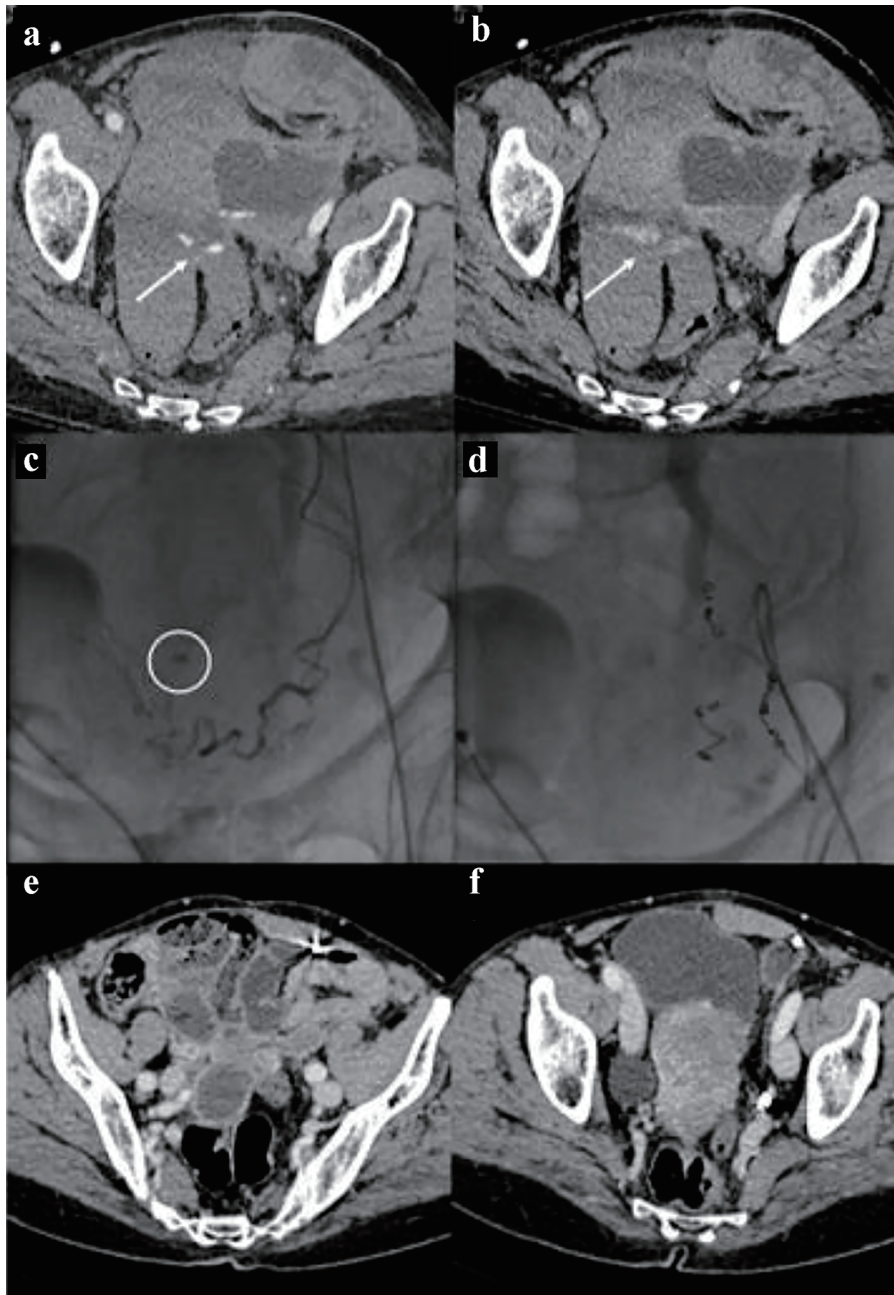


Figure 1. Bleeding in the context of the left uterine broad ligament. The CT images in (a) and (b) show the spots of active bleeding (arrows) with progressive spread of contrast medium. The angiographic image in (c) shows the active bleeding spot adjacent to the left uterine artery. The angiographic image in (d) shows the complete embolization, by means of metallic micro-spirals, of the arterial afferents at the bleeding point. CT images in (e) and (f) show complete reabsorption of hematomas after 3 months. CT: computed tomography.

COVID-19 SS, PLT count, INR, SAT area, and VAT/SAT ratio; INR tends to be higher in the embolization group, although in a non-significant way. There was a slightly significant difference in BMI between embolization and non-embolization groups, with lower values in the former. There was a significant difference in sex between embolization and non-embolization groups, with a higher number of females compared to males in the former group ($P \leq 0.05$). A statistically significant

difference was observed between the embolization and non-embolization groups for VAT area, with smaller values in the embolization group and a mean difference of 64.2 cm^2 (95% CI: 8.3 - 120.1; $P < 0.05$). Results are listed in Tables 2 and 3. The multivariate logistic regression analysis showed a statistical significance comparing TAE and non-TAE groups for sex (TAE was more frequently performed for male) and PLT (TAE was more frequently performed for patients with lower

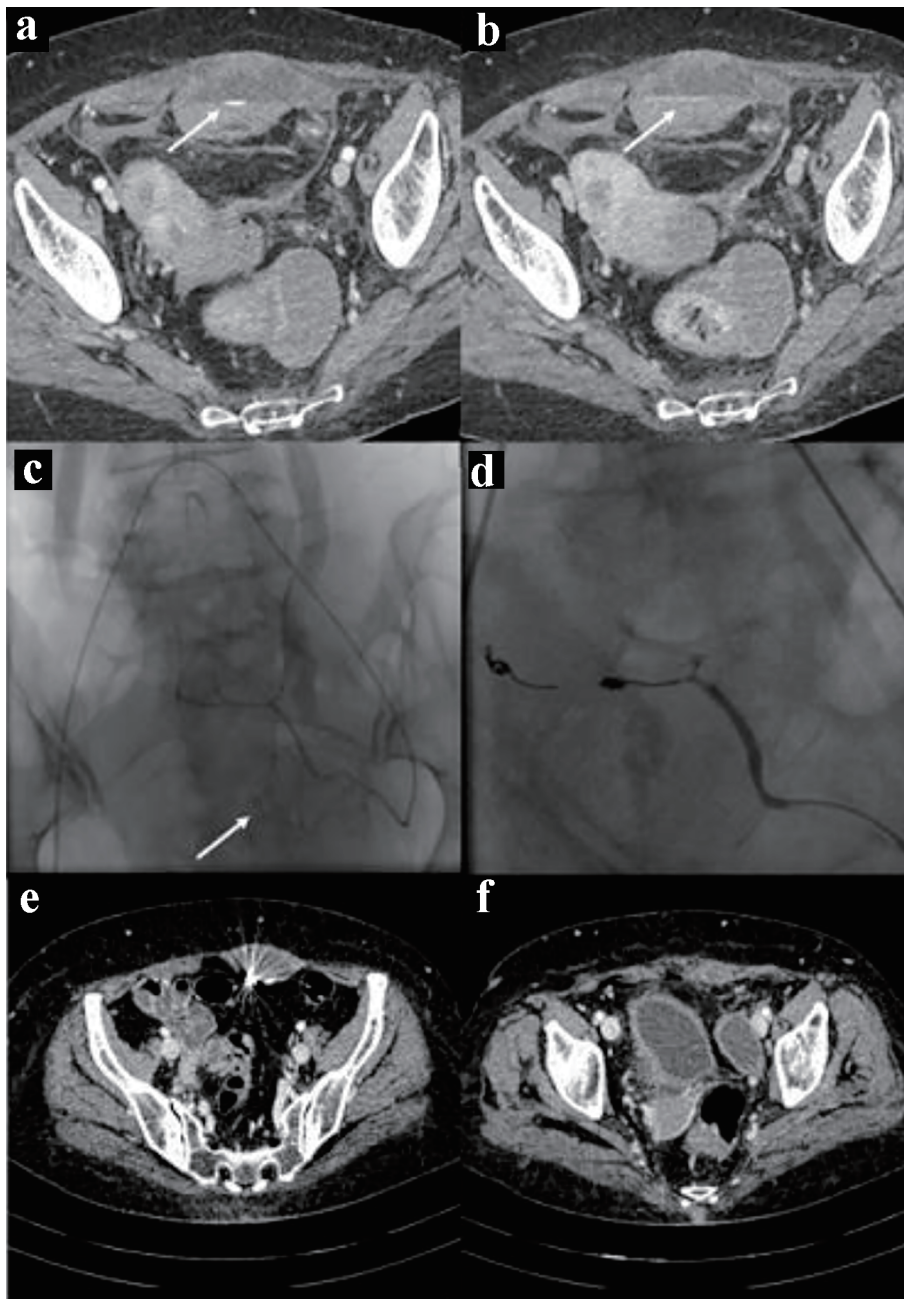


Figure 2. Bleeding in the context of the left rectus abdominis muscle. The CT images in (a) and (b) show the spots of active bleeding (arrows) with progressive spread of contrast medium. The angiographic image in (c) shows the active bleeding spot (arrow) adjacent to the left inferior epigastric artery. The angiographic image in (d) shows the complete embolization, by means of glue and metallic micro-spirals, of the arterial afferents at the bleeding point. CT images in (e) and (f) show complete reabsorption of hematomas after 3 months. CT: computed tomography.

PLT count) (Table 4); the difference in values among bleeding and non-bleeding groups was significant only for BMI (Table 4).

Discussion

The bleeding phenomenon in patients affected by COVID-19

is of crucial importance for their clinical management and prognosis [6, 9, 10]. The bleeding events are the results of a series of clinical and therapeutic factors depending on the intrinsic characteristics of the infection and the standard therapeutic strategies implemented to manage the occurrence of thrombotic events [8]. Given the importance of the association between obesity and the clinical outcome in patients with SARS-CoV-2 infection [13, 14, 18], we aimed to analyze the

Table 1. Soft Tissue Bleeding Features and Embolization Techniques

Soft tissue bleeding features	No. of patients
Bleeding site	
Iliopsoas muscle	16
Rectus abdominis muscle	12
Quadriceps femoris muscle	4
Adductor magnus muscle	4
Soleus muscle	2
Triceps brachii muscle	5
Biceps brachii muscle	3
Upper abdomen	8
Pelvic floor	6
Serratus anterior muscle	4
Pectoralis minor muscle	2
Masseter muscle	2
Scalene muscles	2
Embolization techniques	
Coils	4
Glue	2
Gelfoam	2
Coils + gelfoam	2
Coils + glue	2
Coils + microparticles	4

relationship between the onset of soft tissue bleeding events and the amount of adipose tissue measured through CT scan analysis; measurements are not routinely performed in clinical practice and was our goal to assess their usefulness for predicting the bleeding risk in COVID-19 patients in an experimental setting. We considered the need for TAE treatment as an additional factor to determine the complexity of soft tis-

Table 2. Variables for Bleeding Group and Control Group

Variables	Bleeding group	Control group	P
No. of patients	70	62	
Sex (male/female)	50/20	46/16	> 0.05
Age (mean ± SD) (years)	70.9 ± 11.6	65 ± 11.2	< 0.05
COVID-19 SS	12.5 ± 4.7	14.6 ± 4.5	> 0.05
BMI (kg/m ²)	26.6 ± 3.7	29.6 ± 4.9	< 0.05
PLT count (× 10 ⁹ /L)	235.3 ± 91.2	254 ± 75.6	> 0.05
INR	1.3 ± 0.3	1.2 ± 0.2	> 0.05
SAT area (cm ²)	136 ± 78	159 ± 82.2	> 0.05
VAT area (cm ²)	168 ± 84.6	196 ± 101.9	> 0.05
VAT/SAT	1.5 ± 0.8	1.5 ± 0.9	> 0.05

COVID-19: coronavirus disease 2019; SS: severity score; BMI: body mass index; PLT: platelet; INR: international rationalized ratio; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue.

Table 3. Variables for Embolization Group and Non-Embolization Group

Variables	Embolization group	Non-embolization group	P
No. of patients	16	54	
Sex (male/female)	6/10	44/10	< 0.05
Age (mean ± SD) (years)	72.6 ± 6.2	70.4 ± 12.8	> 0.05
COVID-19 SS	10.1 ± 4.6	13.2 ± 4.5	> 0.05
BMI (kg/m ²)	25.3 ± 4	27.4 ± 3.6	< 0.05
PLT count (× 10 ⁹ /L)	276.1 ± 65.7	222.7 ± 95.2	> 0.05
INR	1.4 ± 0.5	1.2 ± 0.2	> 0.05
SAT area (cm ²)	105.6 ± 63.2	145 ± 80.7	> 0.05
VAT area (cm ²)	118.5 ± 58.4	182.7 ± 86.4	< 0.05
VAT/SAT	1.4 ± 0.7	1.6 ± 0.8	> 0.05

COVID-19: coronavirus disease 2019; SS: severity score; BMI: body mass index; PLT: platelet; INR: international rationalized ratio; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue.

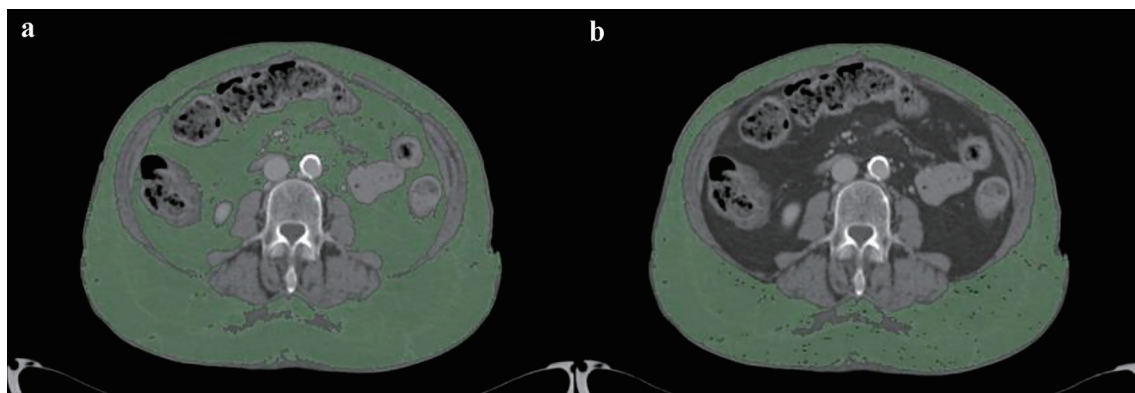


Figure 3. Measurement of adipose tissue areas in cm² obtained by analyzing axial CT images at the level of the third lumbar vertebra with an image processing application (OsiriX, Pixmeo, Bernex, Switzerland): TAT (a) and SAT (b). VAT is calculated by difference between TAT and SAT. CT: computed tomography; TAT: total adipose tissue; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue.

Table 4. Multivariate Logistic Regression Analysis for Bleeding and Control Groups and for Embolization and Non-Embolization Groups

Variables	Score	df	Significance
Bleeding and control groups			
Age	0.646	1	0.421
Sex	15.086	1	< 0.001*
BMI	1.839	1	0.175
PLT	7.189	1	0.007*
INR	0.024	1	0.877
Hb	0.003	1	0.955
Overall status	18.505	6	0.005
Embolization and non-embolization groups			
Age	0.063	1	0.802
Sex	2.182	1	0.140
BMI	13.603	1	< 0.001*
PLT	0.631	1	0.427
INR	2.064	1	0.151
Hb	3.823	1	0.051
Overall status	16.871	6	0.010

*Significance was set at 0.05. BMI: body mass index; PLT: platelet; INR: international rationalized ratio; Hb: hemoglobin.

sue bleeding [11]. Our results show that, although factors such as age are related to a higher risk of soft tissue bleeding events according to an overall increased risk of worse prognosis in elder people [3], bleeding in COVID-19 patients is not dependent on the amount of adipose tissue. In our population, a lower amount of VAT in patients with soft tissue bleeding who required TAE was observed, compared to patients undergoing medical treatment alone in the bleeding group. Even more, a tendency to a lower amount of VAT and SAT in patients with bleeding compared to the control group was counted. A lower BMI was also observed in the bleeding group compared to the control group and in the embolization group compared to the non-embolization group. Literature data show a worse overall prognosis of obese patients or those with greater amounts of visceral fat, presumably determined by inflammatory and metabolic factors [20, 24]. Our work shows that soft tissue bleeding phenomenon occurs most frequently in elderly patients [25] and that unstable bleedings requiring TAE are most frequent in patients with lower VAT. We hypothesize that complicated bleedings have a pathogenesis mechanism related to microtraumatic injuries to soft tissues rather than the patient's fat mass. It is well known that non-self-limiting bleedings are more frequently associated with muscle lesions [26, 27], often caused by the only mobilization on COVID-19 patients, on which anticoagulant therapy is an additive risk factor [28, 29]. We assume that, most likely, a greater fat mass can have a containing function on bleeding by limiting its progression in surrounding structures. In conclusion, our data suggest that soft tissue hemorrhagic events in COVID-19 patients are not easily predictable but it may be more frequent to find them in elderly patients and with a major severity in patients with

low VAT. This study has some limitations including poor patient population, poor comparison with literature data due to the relative recent spread of the disease, lack of subdivision of bleeding by site and contributing cause; for a better understanding of soft tissue bleeding in COVID patients, prospective studies and case-control analyzes with more detailed grouping are needed. Perhaps it might be interesting to know how long after the start of anticoagulant therapy and from the diagnosis of the pathology the bleeding phenomenon began.

In conclusion, our results show that soft tissue bleeding in COVID-19 patients is more frequent and more severe in patients with low BMI and amount of VAT, demonstrating that the fat mass may have a containing function on bleeding by limiting its progression in surrounding structures. There are some other factors in our series that influence the risk of bleeding, such as age, thromboprophylaxis therapy and BMI. We should also keep in mind the concomitance of anticoagulant therapy in all COVID-19 patients and the complexity of hemodynamic system in these patients, which can affect the generalization of the results.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

All authors declare that they have no conflict of interest.

Informed Consent

Informed consent was obtained from all subjects involved in the study at the time of CT execution.

Author Contributions

Eliodoro Faiella: guarantor of integrity of the entire study, study concepts and design; Gennaro Castiello: study concepts and design, manuscript preparation; Domiziana Santucci: manuscript editing; Giuseppina Pacella: manuscript preparation; Caterina Bernetti: literature research, manuscript preparation; Moises Muley Villamu: clinical studies; Raffaele Antonelli Incalzi: supervision; Bruno Beomonte Zobel: data analysis, supervision; Carlo Cosimo Quattrocchi: English editing and revision; Rosario Francesco Grasso: supervision.

Data Availability

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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