MSD

Medical Science and Discovery
ISSN: 2148-6832

Spontaneous hematomas, the new surgical challenge of COVID patients? Hematomas in COVID patients

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ABSTRACT

Objective: There was a critical inconsistency in making therapeutic choices regarding anticoagulation in patients with COVID-19. This study aims to evaluate and determine the causes that led to the formation of hematomas, spontaneous bleeding or what is involved in this hypothesis and the elements related to this aspect.

Patients and methods: The present study is a case series analysis that aims to identify and verify the cause of spontaneous hematomas in COVID positive patients for whom surgery was required. Thus, we analysed patients who presented various spontaneous hematomas during the covid pandemic (March 2020 - May 2021) for which surgery was performed, having as a control group (CG) a homogeneous group in terms of age, covid infection severity, and comorbidities with the study group (SG).

Results: Regarding the preoperative and postoperative days, SG had average values of 4.76±5.36 (Mean±SD) for preoperative days and 9.5±9.327 for postoperative days. Given that one of the most suspected causes of hematomas was considered an anticoagulant overdose, we compared the anticoagulant doses and the type of anticoagulant, so the anticoagulant doses did not show statistically significant differences (0.836±0.294ml in SG versus 0.866±0.343ml in CG with p=0.588). As expected, hemoglobin (Hb) was significantly lower for SG with mean values of 7.266±1.431mg/dl compared to CG that had mean values of 12.9±2.092mg/dl (p=0.001). The correlation between the value of Hb (average value was 12.9 mg/dl, a minimum of 8.7 mg/dl and a maximum of 16.6 mg/dl) and the value of procalcitonin (average value was 0.13, a minimum of 0.02 and a maximum of 0.7) is statistically significant having p=0.012. In SG, hemoglobin can be correlated with ESR (erythrocyte sedimentation rate), p=0.008 and with procalcitonin, p=0.05. Both have a negative correlation explained by a proinflammatory status that can aggravate low hemoglobin levels, but without a direct link to high ESR and procalcitonin values.

Conclusions: The hypothesis of anticoagulant overdose is not supported or verified by the present study, we consider that additional thromboelastography tests are necessary to be able to completely refute it. Mortality did not increase statistically significantly.

Keywords: COVID-19, hematomas, hemostasis,

Research Article

Received 11-04-2022

Accepted 16-05-2022

Available Online: 20-05-2022

Published 30-05-2022

INTRODUCTION

The World Health Organization (WHO) named the newly found coronavirus in 2019 ”COVID-19” and later declared it a pandemic in March 2020. General clinical signs of SARS-CoV-2 disease include fever, myalgia, weakness and it can go up to dyspnea and pneumonia. Also, it associates other disorders from the gastrointestinal area (vomiting, nausea), cardiovascular (myocardial infarction, arrhythmias) and renal (acute renal injury). Recent reports and studies also point to vascular damage that includes thrombosis and endothelial dysfunction [1-3].

Since the beginning of the COVID pandemic, there have been multiple studies in this direction, studies that have identified the procoagulant status of this infection, which is why anticoagulation was introduced in the treatment protocol.

As the focus on coagulopathy caused by COVID-19 increases, mortality can be explained by thrombotic phenomena [1,2].

http://dx.doi.org/10.36472/msd.v9i5.718

A multicenter review in the United States detailed a thrombotic complication rate of 9.5%, despite the administration of the standard dose of prophylactic anticoagulation [3]. Furthermore, bleeding episodes have been identified in patients with COVID-19. In general, the number of patients with complications that lead to death varies from 4.8% to 8% [3, 4].

The early stage of this disease can be associated with high D-dimer, prolonged PT, and elevated levels of fibrinogen, indicating activation of coagulation pathways and thrombosis (Mehrdad Rostami)

Elevated plasma levels of CRP (C-reactive protein) and NT-proBNP (N-terminal B-type natriuretic peptide) are fully related to the lethal outcome of COVID-19, suggesting that irritation is a potent component of myocardial injury and underlying disease of mortality [2].

The disease progresses in 3 stages: the initial disease caused by dynamic contamination, an aspiration moment stage and, when extreme, a third stage characterized by hyperinflammation, cytokine storm, high levels of biomarkers of heart damage and remarkable morbidity and mortality. In some patients with COVID-19, the inflammatory reaction continues to intensify and it occurs in systemic inflammation, with a better measure on deceased people with dynamic thrombocytopenia. Regarding this famous decrease in platelet count, clots have been identified in the small vessels of the lungs, heart and liver of patients with COVID-19 [4] and extend the predominance of deep vein thrombosis in hospitalized patients with dynamic contamination [3, 5].

There is no current standardized approach to anticoagulation in patients with SARS-CoV-2 infection, while the potential dangers of death remain. Our thinking characterizes the anticoagulation therapy used in patients with COVID-19 and the associated death risk [2, 6].

There was a critical inconsistency in making therapeutic choices regarding anticoagulation in patients with COVID-19. It is well known that anticoagulation therapy is a non-lethal treatment with regular clinical controls. The choice to increase anticoagulation doses should subsequently be carefully considered. The dangers should be communicated, and the sharing of choices is ideal in such clinical situations [2, 7].

Through this study, we aimed to evaluate and determine the causes that led to the formation of hematomas, spontaneous bleeding or what is involved in this hypothesis and what the elements related to this aspect are

MATERIAL and METHODS

The present study is a case series analysis that aims to identify and verify the cause of spontaneous hematomas in COVID positive patients for whom surgery was required. Thus, we analyzed patients who presented various spontaneous hematomas during the covid pandemic (March 2020 - May 2021) for which surgery was performed having as a control group (CG) a homogeneous group in terms of age, COVID-19 severity and comorbidities with the study group (SG). Covid severity, O2 requirement, age, sex, hospitalization time (both preoperative and postoperative), discharge status, comorbidities, and biological analyzes (complete blood count, coagulation testing, D-dimer) were analyzed for both groups. The data were collected from patients' files and from the digitized database of the 'Saint John' Emergency Clinical Hospital, Bucharest for the period March 2020 - May 2021. Descriptive and analytical statistics were performed using Microsoft Excel and SPSS Statistics 17.0 considering as statistically significant a p-value <0.05, all values being expressed in mean and standard deviation.

RESULTS

The SG group, the group of patients who underwent surgery for a spontaneous hematoma, had an average age of 70.83± 8.009 years. The CG was chosen to be uniform with the study group and presented an average age of 72.33 ±6.321 years. Also, the ratio of patients by gender was similar according to the graph below.(Figure 1)

Regarding the preoperative and postoperative days, SG had average of 4.76 ± 5.36 for preoperative days and 9.5± 9.327 values for postoperative days.

The total hospitalization days are the common parameter of the two groups, we compared them, and we obtained the following values: 14.17± 10.188 days for SG versus 14.93± 4.096 days for CG. This shows us that there is no statistically significant difference between the two groups and therefore, the appearance of a hematoma that required surgery did not prolong the total number of days of hospitalization. Also, for SG there is a statistically significant correlation between age and total days of hospitalization (p=0.049).

The state of discharge is shown according to the graphs below, in CG there were no deceased patients, although the severity of SARS-CoV2 pneumonia was similar for both groups. For SG, most patients (n=8) died, thus the comparative data between the two groups was statistically significant (p = 0.002). Also, for CG, there is a correlation between total hospitalization days and status upon discharge (p=0.005) meaning that a longer stay in hospital can negatively influence the discharge status. (Figure 2)

Given that one of the most suspected causes of hematomas was considered an anticoagulant overdose, we compared the anticoagulant doses and the type of anticoagulant, so the anticoagulant doses did not show statistically significant differences (0.836 ±0.294ml in SG versus 0.866 ±0.343ml in CG with p=0.588). Given that the type of anticoagulant used (Fraxiparin, Clexane or Heparin) was evenly distributed in the two groups, we cannot conclude that this was the cause of the hematomas.

As expected, hemoglobin (Hb) was significantly lower for SG, with mean values of 7.266 ±1.431mg/dl compared to CG which had mean values of 12.9 ±2.092mg/dl (p=0.001). The correlation between the value of Hb (average value was 12.9 mg/dl, a minimum of 8.7 mg/dl and a maximum of 16.6 mg/dl) and the value of procalcitonin (average value was 0.13, a minimum of 0.02 and a maximum of 0.7) is statistically significant having p=0.012. In SG, hemoglobin can be correlated with ESR (erythrocyte sedimentation rate), p=0.008 and with procalcitonin, p=0.05. Both have a negative correlation explained by a proinflammatory status that can aggravate low hemoglobin levels, but without a direct link to high ESR and procalcitonin values. (Figure 3)

http://dx.doi.org/10.36472/msd.v9i5.718

The difference in the number of leukocytes between the two groups was also with a statistical significance, SG had much higher values than those in CG (19.065 ±897/µl in SG vs 8.961 ±4.356/µl in CG) thus, we can raise the hypothesis that proinflammatory and infectious status can cause a more important state of anticoagulation. We also observed that patients in CG have lower values of leucocytes (average value was 8.96/µl, with a minimum of 2.77/µl and a maximum of 18.9/µl) also had a lower value of thrombocytes (average value was 346.000/µl with a minimum of 59.000/µl and a maximum of 890.000/µl), p=0.012. Leucocytes also correlate with C-reactive protein (average value was 36.64mg/dL with a minimum of 0.63 mg/dL and a maximum of 204 mg/dL), p= 0.012, being a statistically significant correlation. Another correlation was made in SG between preoperative days and the number of leucocytes (p=0.007) explained by the proinflammatory status, an increased number of leukocytes causing the operating team to operate earlier, even if the proinflammatory status could be given by the pneumological condition. Also, C-reactive protein was correlated with procalcitonin (p=0.046), both being involved in the proinflammatory status. (Figure 4)

The values of fibrinogen in CG (average value was 435 mg/dL with a minimum of 276 mg/dL and a maximum of 613 mg/dL) have a statistically significant correlation with procalcitonin (average value was 0.13, a minimum of 0.02 and a maximum of 0.7), p= 0.032 and with IL-6 (average value was 98.8 pg/mL with a minimum of 1.5 pg/mL and a maximum of 507 pg/mL), where p= 0.05.

Another correlation in CG was D-dimers (average value was 0.64 with a minimum of 0.27 and a maximum of 1.81) with IL-6 (average value was 98.8 µg/mL with a minimum of 1.5 µg/mL and a maximum of 507 µg/mL), p= 0.005. The higher the D-dimers was, the higher the value of IL-6 was. (Figure 5)

Moving to coagulation, in the same CG we also observed that aPTT (activated partial thromboplastin time), with an average value of 38s (a minimum of 22.4s and a maximum of 99s) has a more statistically significant correlation with fibrinogen (p=0.03), with ESR (average value was 43s with a minimum of 11s and a maximum of 89s), p=0.029, with procalcitonin (p= 0.001). We observed that IL-6 (average value was 98.8 with a minimum of 1.5 and a maximum of 507) has some interesting statistically significant correlation with the total hospitalization days (average value was 15 with a minimum of 11 and a maximum of 25), p=0.008, also with fibrinogen,(p= 0.05) and with D-dimer (p= 0.005).

Regarding platelets, in SG there is a negative correlation between them and age (p=0.022), also thrombocytes with ESR (p=0.046). This is explained by the procoagulant status in the context of sepsis, elderly patients consume platelets faster and cannot be produced in time due to age slowdown. (Figure 6)

In the case of the anticoagulant dose (average value was 0.9ml with a minimum of 0.4ml and a maximum of 1.6ml), we found that there is a statistically significant correlation with the total hospitalization days (p=0.05) and with Hb (p=0.05). It is known that the dose of anticoagulant increases aPTT, this being a positive correlation in SG with p=0.044. (Figure 7)

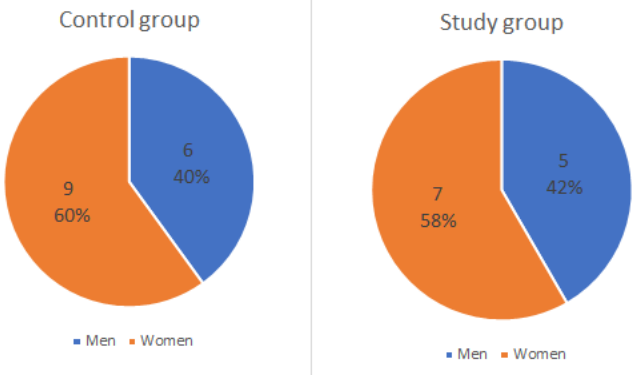

Figure 1: Gender division of the two groups

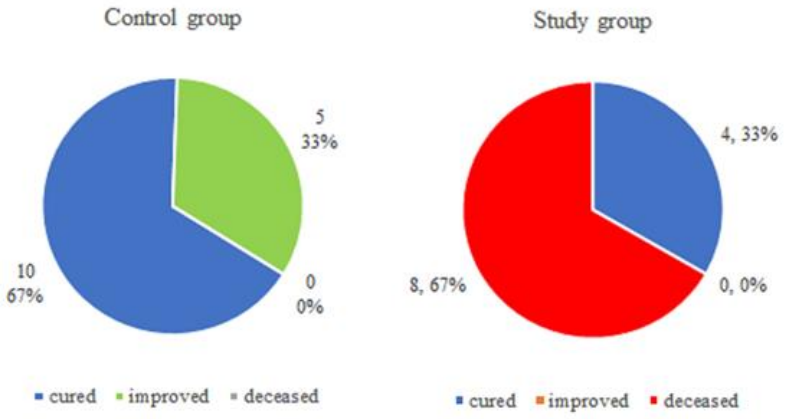

Figure 2: State of discharge for the two groups (cured/improved/deceased)

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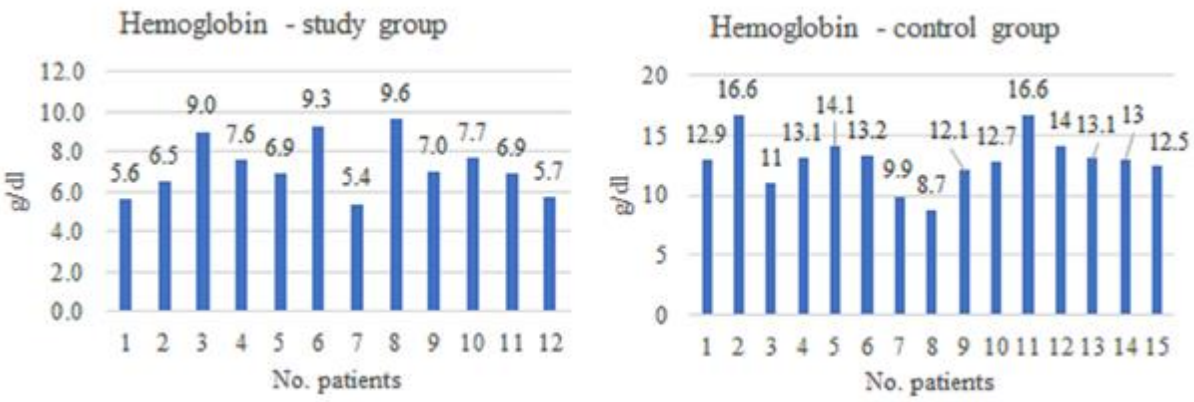

Figure 3: Hemoglobin evaluation for the two groups

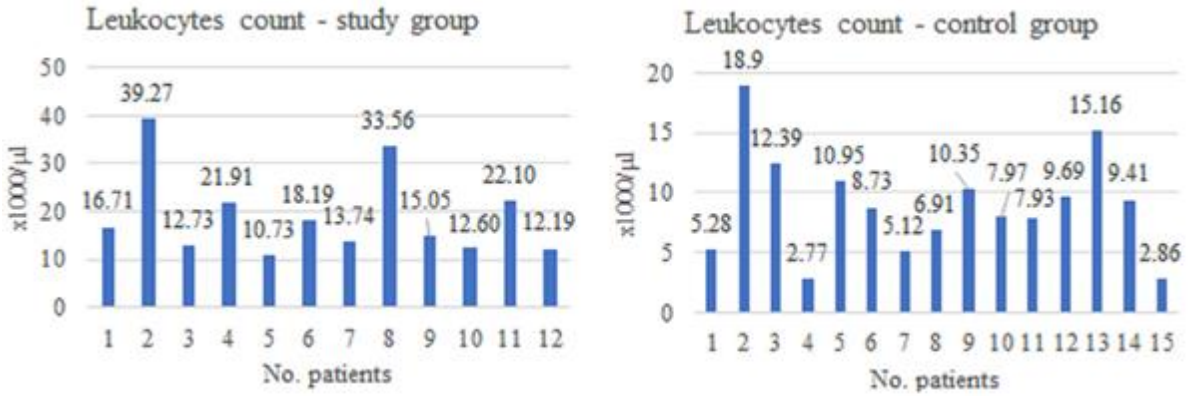

Figure 4: Leukocytes evaluation for the two groups

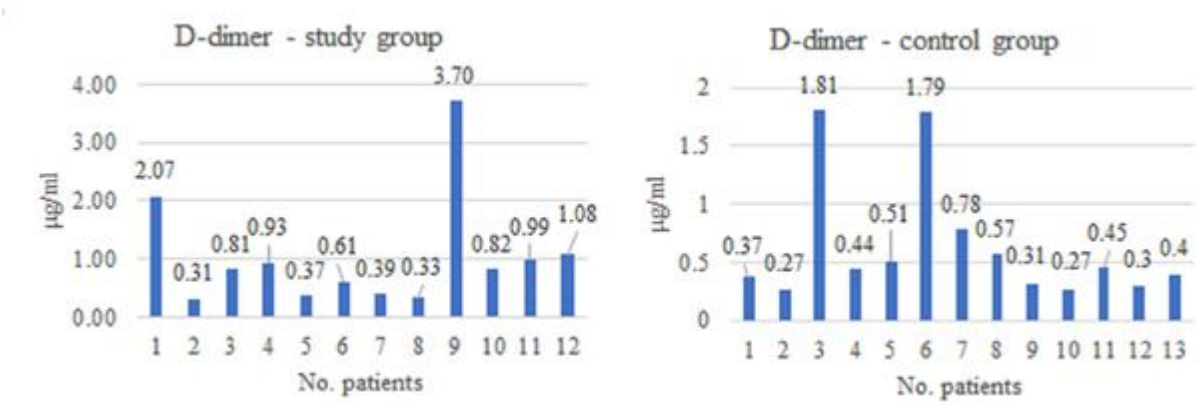

Figure 5: D-Dimers evaluation for the two groups

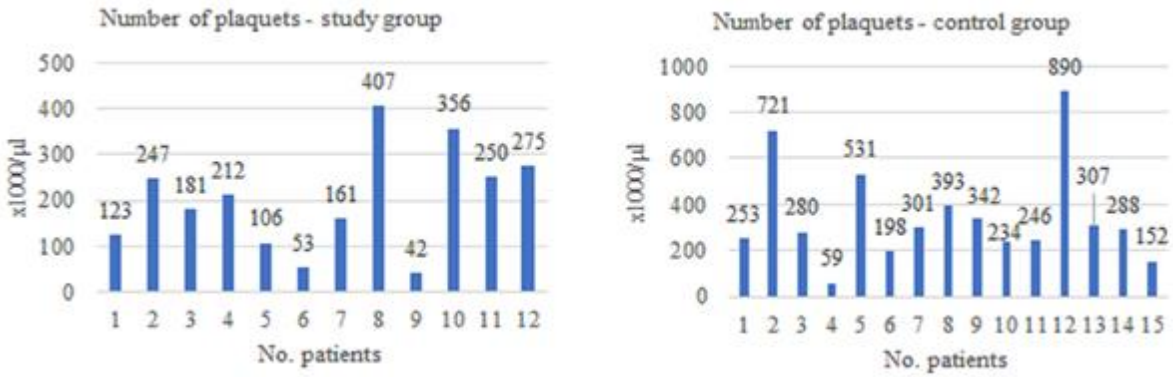

Figure 6: Platlets count evaluation for the two groups

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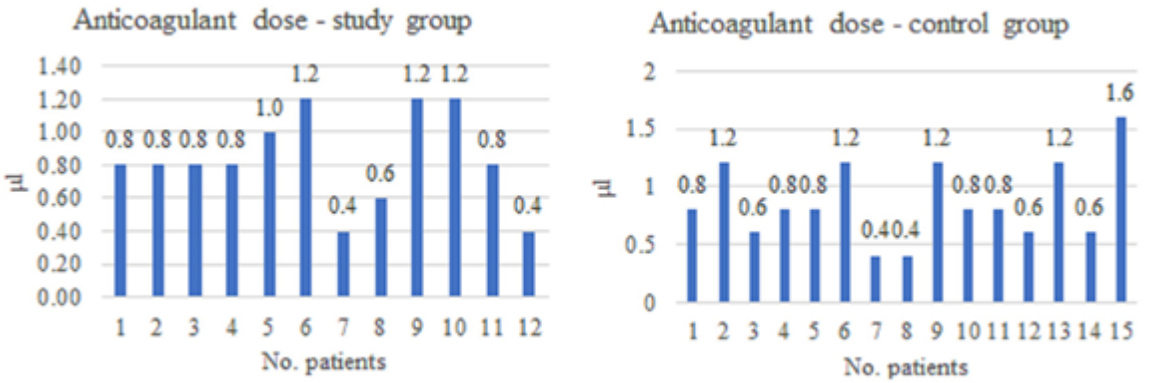

Figure 7: Anticoagulant dose evaluation for the two groups

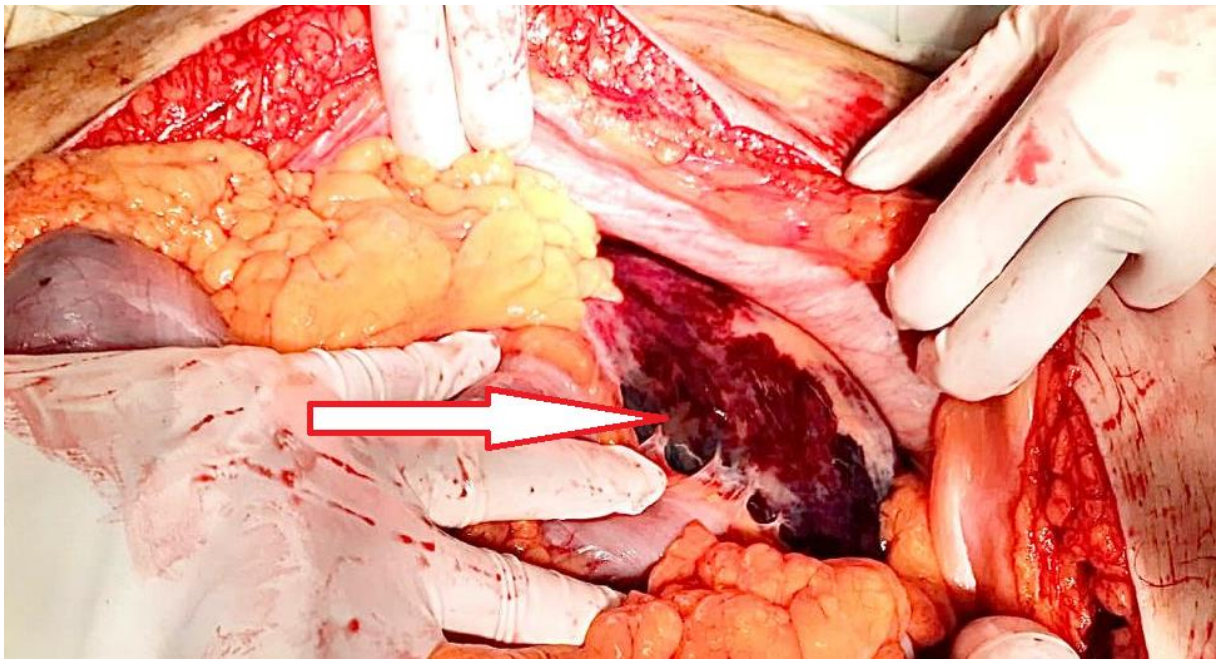

Figure 8: Retroperitoneal hematoma of the psoas muscle migrating to the pelvis

DISCUSSION

The main hypothesis studied both in the literature and in our study was that of the modified coagulation status within SARS-COV 2 infection. In the literature, 61% of patients were being treated with prophylactic doses of anticoagulation, while 7% and 29% were treated with sub-therapeutic and therapeutic anticoagulation (TA) doses, respectively. In 44% of patients, Musoke et al. found that the decision to escalate the dose of anticoagulation was based on laboratory values characterizing the severity of COVID-19 such as rising D-dimer levels. There were significantly higher rates of bleeding from non-CNS/non-GI sites ($p = 0.039$) and from any bleeding site overall ($p = 0.019$) with TA. TA was associated with significantly higher rates of inpatient death (41.6% vs 15.3% $p < 0.0001$) compared to those without [2].

What is noteworthy is the fact that both in the literature and in our study, the extremely serious cases that presented hematomas, also had an extremely severe COVID infection even with the association of IVCS. Critically ill patients with COVID-19 experience high rates of venous and arterial thrombotic complications.

The rates of bleeding may be higher than previously reported and re-iterate the need for randomised trials to better understand the risk-benefit ratio of different anticoagulation strategies. The International Society of thrombosis and hemostasis (ISTH) implemented DIC score, which takes into account INR value, fibrinogen, D-Dimers and platelets count, and established a score of risk for DIC [1,3].

This study by a team of surgeons highlights the importance of surgery in the treatment of this condition. The surgeon has a defining role in diagnosing and treating this pathology. First of all, he must make the differential diagnosis of hematomas with other pathologies with similar manifestations (neoplasms, digestive hemorrhages, inguinal hernias, etc.). Secondly, he must determine the urgency of these hematomas if there is active bleeding or it has stopped and conservative treatment may be attempted if the hematoma is not significant. Last but not least, it plays an extremely important role in draining and evacuating the hematoma through surgery (**Figure 8** - Retroperitoneal hematoma of the psoas muscle migrating to the pelvis)

There is currently available evidence that suggests the COVID-19 coagulopathy is an association of localized pulmonary platelet consumption, low-grade DIC (but rarely meeting the ISTH DIC criteria) and in some instances a thrombotic microangiopathy.

For the two groups, we evaluated the ISTH criteria for DIC (disseminated intravascular coagulation), and we noted no significant difference considering this parameter (p-value=0.0919). DIC does not influence the bleeding in CG and SG. It is proven that DIC can translate to transitory thrombocytopenia, but in our groups, only one patient (in the SG) had a score >5.

Severe COVID-19 illness is associated with increased platelet activation as well as platelet-monocyte aggregation. Platelets from severely ill COVID-19 patients can amplify inflammation and affect coagulability in these patients.

Incriminating COVID-19 for the coagulopathy associated with bleeding and hematomas, one does not forget that all severe infectious disorders are associated with changes in hemostasis laboratory values as well as thrombotic and bleeding events [8, 9]. Before the COVID-19 era, there were some hematomas, but the number was negligible compared to the rest of the cases.

A hypothesis suggests that bleeding can occur spontaneously [10], but other mechanisms may also imply trauma, as other studies indicate [11,12]. Another study indicates that percutaneous veno-venous extracorporeal membrane oxygenation (ECMO) can lead to hematoma formation [13]. We raise the idea that patient mobilization can also be incriminated – some of the patients included in SG have been transported in multiple units and submitted to multiple investigations. The surgeries represent an increased difficulty due to the associated medical conditions of the patients, technical difficulties given by the protective equipment, and last but not least due to the impossibility to identify a unique, clear source of bleeding, most often the bleeding being a diffuse bleeding [14-17].

Most studies reported that anticoagulant or antithrombotic therapies were used to treat these patients. Before the COVID-19 era, a study published by Gonzalez et al. [14] reported on 23 cases a preponderance of anticoagulated patients (65.21%) in the spontaneous etiology of retroperitoneal hematoma [16 - 18].

If we refer to the received anticoagulant doses, we notice that there are no statistically significant differences between the two groups, which is why we cannot support through our study the hypothesis of anticoagulant overdose as the direct cause of hematomas. We consider that additional thromboelastography tests are necessary in order to have a complete picture of this hypothesis.

Other studies suggested using coil embolization, a minimally invasive procedure [10-12], but in our group patients with hemodynamic instability required emergency surgery. Sahu et. Al [13] found in an analysis on 78 retroperitoneal hematomas that medical management alone can be successful in 59% of cases; which 38% underwent surgery and only 3% radiologic procedures. The same study reported that 2 of the 78 patients (2.56%) died from hemorrhagic shock [19, 20].

The studies of the coagulation cascade revealed by the literature require completion, as the hypothesis of microtraumas must also be studied much more detailed than before, with careful monitoring of these cases [19-21]. As expected, platelet count and hemoglobin levels are two of the variables directly related to the prognosis of these patients.

However, we assume the limitations of the study related to the small number of cases and the additional investigations necessary for molecular conclusions. Despite these limitations, the present study remains the only one in the literature to date with the highest number of cases and a similar control group in terms of gender distribution, age and covid severity.

CONCLUSION

Risk scores must be implemented in order to better identify these patients in order to avoid risky surgery for hemostasis or evacuation of hematomas. As expected, platelet count and hemoglobin levels are two of the variables directly related to the prognosis of these patients.

The surgeries represent an increased difficulty due to the associated medical conditions of the patients, technical difficulties given by the protective equipment and last but not least due to the impossibility to identify a unique, clear source of bleeding, most often the bleeding being a diffuse bleeding.

The hypothesis of anticoagulant overdose is not supported or verified by the present study, we consider that additional thromboelastography tests are necessary to be able to completely refute it.

Author Contributions: RM, CU, AV, DC, RI, MZ, AM, NI, OG: Concept, Data collection and/or processing, Analysis and/or interpretation, Literature review, **RM:** Writing, and Revision.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This article did not receive a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: All procedures performed in this study were in accordance with the ethical standards of the institutional research committee.

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