ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 March 6; 11(7): 1434-1668

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 11 Number 7 March 6, 2023

World Journal of Clinical Cases

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LETTER TO THE EDITOR

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 7 March 6, 2023

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

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PUBLICATION DATE
March 6, 2023

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https://www.f6publishing.com

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World Journal of Clinical Cases

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World J Clin Cases 2023 March 6; 11(7): 1528-1548

DOI: 10.12998/wjcc.v11.i7.1528

ISSN 2307-8960 (online)

CASE REPORT

Retroperitoneal and abdominal bleeding in anticoagulated COVID-19 hospitalized patients: Case series and brief literature review

Delian Evrev, Metodija Sekulovski, Milena Gulinac, Hristo Dobrev, Tsvetelina Velikova, George Hadjidekov

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Chan ASW, China; Nooripour R, Iran

Received: October 10, 2022
Peer-review started: October 10, 2022
First decision: November 18, 2022
Revised: December 17, 2022
Accepted: February 10, 2023
Article in press: February 10, 2023
Published online: March 6, 2023

Delian Evrev, Hristo Dobrev, Department of Cardiac Surgery, University Hospital Lozenetz, Sofia 1407, Bulgaria

Delian Evrev, Metodija Sekulovski, Tsvetelina Velikova, George Hadjidekov, Medical Faculty, Sofia University St. Kliment Ohridski, Sofia 1407, Bulgaria

Metodija Sekulovski, Department of Anesthesiology and Intensive Care, University Hospital Lozenetz, Sofia 1407, Bulgaria

Milena Gulinac, Department of General and Clinical Pathology, Medical University of Plovdiv, Plovdiv 6000, Bulgaria

George Hadjidekov, Department of Radiology, University Hospital "Lozenetz", Kozyak 1 str., Sofia 1407, Bulgaria

Corresponding author: Tsvetelina Velikova, MD, PhD, Academic Editor, Assistant Professor, Medical Faculty, Sofia University St. Kliment Ohridski, Kozyak 1 str., Sofia 1407, Bulgaria. tsvelikova@medfac.mu-sofia.bg

Abstract

BACKGROUND

Hospitalized and severely ill coronavirus disease 2019 (COVID-19) patients necessitate prophylactic or therapeutic anticoagulation to minimize the risk of thrombosis at different sites. Life-threatening bleeding complications include spontaneous iliopsoas hematoma, peritoneal bleeding, and extra-abdominal manifestations such as intracranial hemorrhage.

CASE SUMMARY

Bleeding in the abdominal wall results in less severe complications than seen with iliopsoas hematoma or peritoneal bleeding. In our case series of 9 patients, we present retroperitoneal and abdominal bleeding complications following anticoagulation in hospitalized COVID-19 patients with severe acute respiratory syndrome coronavirus 2 pneumonia. Contrast-enhanced computed tomography (CE-CT) is the best imaging modality for assessing hematoma secondary to anticoagulation and determines the therapeutic approach, whether interventional, surgical, or conservative management.

CONCLUSION

We present the role of CE-CT for rapid and precise localization of the bleeding site

and prognostic counseling. Finally, we provide a brief review of the literature.

Key Words: COVID-19; Retroperitoneal bleeding; Abdominal bleeding; Anticoagulation drugs; COVID-19 hospitalized patients; Case report; Case series

Core Tip: Hospitalized patients with coronavirus disease 2019 (COVID-19) possess a higher risk for both hypercoagulable state and thrombotic complications due to an imbalance in platelet production and destruction and coagulation system disorders that accompany the pathophysiology of this disease. In line with this, the indication of performing contrast-enhanced multidetector computed tomography may help to identify active hemorrhage as a complication of anticoagulant therapy in hospitalized patients with COVID-19 pneumonia. In addition, pre-contrast scans may define the size and the precise location of suspected hematoma, especially when ultrasound findings are inconclusive.

Citation: Evrev D, Sekulovski M, Gulinac M, Dobrev H, Velikova T, Hadjidekov G. Retroperitoneal and abdominal bleeding in anticoagulated COVID-19 hospitalized patients: Case series and brief literature review. *World J Clin Cases* 2023; 11(7): 1528-1548
URL: https://www.wjgnet.com/2307-8960/full/v11/i7/1528.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i7.1528

INTRODUCTION

As of the beginning of October 2022, 615 million cases of coronavirus disease 2019 (COVID-19) have been reported globally, with 6.5 million fatalities[1]. Hospitalized patients with COVID-19 possess a higher risk for hypercoagulable state and thrombotic complications. The pathophysiology behind this has been suspected to result from increased proinflammatory cytokines such as interleukin-6 (IL-6), IL-1 beta and tumor necrosis factor alpha[2]. The possible causes for this phenomenon are due to hemostatic changes as a direct effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or as a result of cytokine storm that changes (remodels) the onset of systemic inflammatory response syndrome, as seen in other viral diseases[3-5].

Moreover, the prolonged hospital stays with immobilization, corticosteroid use, and dehydration in severely ill patients also contribute to thrombotic events at different sites. Therefore, according to different guidelines[6] and recommendations from accredited institutions and randomized controlled trials, prophylactic or therapeutic anticoagulation is recommended or mandatory in moderate and severely affected patients with COVID-19, respectively[7-11].

Although hypercoagulability and thrombotic events are common, various bleeding complications can occur due to predisposing factors such as the use of anticoagulants and antiplatelets, thrombocytopenia, hyperfibrinolytic state, and consumption of coagulation factors[8,9]. Additional risk factors include age, high body mass index, critically ill status, dialysis, *etc*[10]. From the pathological and critical care medicine points of view, severe bleeding complications, which can be life-threatening, include spontaneous retroperitoneal hematoma (SRH), intra- or extraperitoneal bleeding, and gastrointestinal or intracranial hemorrhage. These complications are also thought to be related to the effects of SARS-CoV-2 on mucosae[12]. Rectus sheath hematomas (RSHs) are less dramatic, but have potential for major blood loss.

Unfortunately, the mechanisms by which coronavirus causes severe damage to organs and fatal complications are still unclear. According to literature and statistics, there are currently about 1.86 million deaths reported as being caused by complications of coronavirus infection, and the leading cause of death in these cases remains acute lung damage leading to respiratory failure[13]. However, SARS-CoV-2 infection may also be associated with coagulopathy, suggested by findings consistent with infection-induced inflammatory changes in blood vessels. To this end, there are frequently described cases of thromboembolism in COVID-19 patients, with more than half exhibiting deep thrombosis of the lower extremities at autopsy[14-16].

COVID-19 patients are prone to both hemostasis alterations and risk of thrombosis or bleeding, as well as complications associated with anticoagulation. However, retroperitoneal and intraabdominal hemorrhages have also occurred, and bleeding manifestations clearly connected to COVID-19, even in those without disseminated intravascular coagulation, have been reported in several studies[17,18]. Therefore, it is critical to highlight potential problems connected with COVID-19 therapy. Furthermore, based on the research available, we should retain a heightened concern for spontaneous bleeding in COVID-19 patients with nonspecific abdominal discomfort or are taking therapeutic dosages of antico-

agulation[19]. As such, it is crucial to have a potent tool to diagnose and manage these clinical situations.

Thrombocytopenia and low fibrinogen, common in patients with COVID-19, appear to be associated with an increased risk of hemorrhage and in-hospital mortality. According to our research and other recently published reports, the most likely major cause of these bleeding complications in patients with severe SARS-CoV-19 infection is cytokine storm syndrome associated with immune disorders[20,21].

In other words, COVID-19 patients are at increased risk of both thrombosis and bleeding due to an imbalance in platelet production and destruction along with other coagulopathies[22-25]. These are possibly affected by the systemic inflammatory response, which causes an imbalance between procoagulant and anticoagulant homeostatic mechanisms. Unfortunately, as of now we have insufficient data on the underlying pathophysiology and do not have any protocol for managing hemostatic alterations in COVID-19 patients.

Recently, some authors have found evidence that the virus can directly infect endothelial cells and promote inflammation. Furthermore, angiotensin converting enzyme -2 receptor is not only expressed by pneumocytes, but also by endothelial cells, activation of which may favor endothelial damage and changes in vascular permeability[17]. Thus, it follows that endothelial damage can be caused either by direct viral infection of the endothelium or an immune-mediated response that ultimately leads to endothelial dysfunction associated with apoptosis and cell death[26]. In addition, endothelial inflammation can cause vasoconstriction with subsequent organ ischemia and a change in homeostatic mechanisms.

Such inflammation of the vascular wall could lead to impaired vascular integrity and the potential development of aneurysms, which can be complicated by rupture. Although the underlying mechanism is unclear, active monitoring and balanced therapy in these patients are highly recommended to manage the risks of thromboembolism and bleeding and help clinicians make a personalized decision in each case. Importantly, retroperitoneal hematoma is not a common radiologically detected consequence of COVID-19, with only a few case studies reported, but may occur in COVID-19 patients on anticoagulation[19,24,27-29]. Additionally, some conditions related to defective hemostasis are challenging to diagnose, and treatment management may be complicated by any comorbidities present.

The indication for performing contrast-enhanced multidetector computer tomography (CE-CT) is concern for active hemorrhage as a complication of anticoagulant therapy in hospitalized patients with COVID-19 pneumonia, as we showed previously[30]. In addition, pre-contrast scans may define the size and precise location of the suspected hematoma, especially when ultrasound (US) findings are inconclusive.

Since hemostatic alterations in COVID-19 patients are common, and the diagnostic process is often challenging, we present 11 cases of abdominal bleeding in COVID-19 patients. The role of imaging in the diagnosis and management of abdominal and retroperitoneal bleeding in COVID-19 on anticoagulation patients is crucial; the present case series and review aims to shed light on these important complications.

CASE PRESENTATION

Case summary

We present a series of 11 patients with abdominal bleeding during their hospitalization at University Hospital "Lozenetz" for COVID-19 bilateral pneumonia. These patients had SARS-CoV-2 infection confirmed with real-time reverse transcription polymerase chain reaction testing. All patients provided informed consent, and the study was conducted following the Declaration of Helsinki and the ethics standards of University Hospital "Lozenetz".

In total, 6 of the patients were diagnosed with retroperitoneal hematoma, 4 with RSH (1 bilateral and 2 with extraperitoneal propagation), and 1 with intraperitoneal bleeding. These patients were among 914 COVID-19 patients admitted to our institution from October 1, 2020, to January 1, 2021; the incidence of bleeding in patients hospitalized for COVID-19 pneumonia therefore is 12 cases per 1000 hospitalizations. The male-to-female ratio was 6 to 5, with age ranging between 51 years and 92 years (mean of 74.27 years).

Patient demographic and clinical characteristics, treatments, and outcomes are shown in Tables 1 and 2.

Chief complaints

All 11 patients had fever, myalgia, and asthenia as main complaints. However, their severity progressed during attempted home treatment, prompting presentation to the hospital. Additionally, 3 patients had dyspnea with productive cough, 2 had a loss of appetite, and another had diarrhea at admission.

The patients differ in terms of the length of time from admission to onset of bleeding, ranging from 2 d to 19 d (mean 9.45 d). The major symptoms were abdominal and back pain, with abdominal pain being predominant in RSH and back and lateral abdominal pain in SRH. Besides the pain, one patient with RSH and extraperitoneal hematoma had leg swelling accompanied by profound asthenia due to

Table 1 Case characteristics from the current case series

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age in yr	63	51	74	86	80	92
Sex	Female	Female	Male	Female	Female	Female
Comorbidities	AH, Asthma	AH, renal transplant, CKD, history of abdominal tumor surgery	AH, IHD, Tonsil carcinoma (status post radiation)	AH, COPD, CKD	AH, ischemic stroke	AH
Chronic anticoagulant/antiplatelet use	ASA	No	No	ASA	ASA	ASA
Clinical presentationat admission	Fever, asthenia, myalgia	Asthenia, dyspnea, cough	Fever, asthenia, loss ofappetite	Fever, asthenia, dyspnea	Fever, asthenia, diarrhea	Fever, asthenia, dyspnea, cough
Duration of illness before admission in days	5	20	11	7	7	7
SpO_2 at admission, %	92	94	94	78	87	97
Time from admission to bleeding in days	9	2	5	10	10	6
Type of bleed	Intraperitoneal	RSH, Extra-peritoneal	SRH	RSH	SRH	RSH
Signs and symptoms of bleed	Abdominal pain	Leg edema, asthenia, low hemoglobin	Abdominal pain	Abdominal pain, hypotension, abdominal guarding	Abdominal Pain (lateral)	Low hemoglobin, abdominal swelling
Hemodynamic instability	No	No	No	Yes	No	No
Maximum O_2 therapy prior to bleed	15 L, mask	3-4 L, mask	9 L, mask	4 L, mask	7 L, nasal	OTI
Pulmonary changes	Moderate	Severe	Mild	Mild	Moderate	Moderate
Length of hospitalization (days)	20	15	20	11	25	10
Anticoagulation (prophy-lactic)	LMWH 4000 IU, BID	No	LMWH 4000 IU, BID	LMWH 4000 IU, BID	No	LMWH 4000 IU, BID
Anticoagulation (therapeutic)	No	LMWH 4000 IU, BID	No	No	LMWH 6000 IU, BID	No
Antiplatelet therapy	ASA	No	ASA	ASA	No	No
Steroids	Methyl-prednisolone	Methyl-prednisolone	Dexa-methasone	Methyl-prednisolone	Methyl-prednisolone	Methyl-prednisolone
Bioproduct units (pRBC/FFP)	2/3	4/4	3/2	2/2	No	No
Surgery	No	Yes	No	No	Yes	No
Outcome	Discharged	Discharged	Discharged	Died	Discharged	Died

AH: Arterial hypertension; IHD: Ischemic heart disease; AF: Atrial fibrillation; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; PE: Pulmonary embolism; PM: Pacemaker; ASA: Acetylsalicylic acid; RSH: Rectus sheath hematoma; SRH: Spontaneous retroperitoneal hematoma; OTI: Orotracheal intubation; CPAP: Continuous positive airway pressure; LMWH: Low molecular weight heparin; IU: International unit; BID: Twice daily; pRBC: Packed red blood cells; FFP: Fresh frozen plasma.

blood loss and low hemoglobin levels. Another patient with bilateral RSH was intubated, mechanically ventilated, and sedated when the bleeding occurred. The only symptom in this patient was swelling of the bilateral abdominal rectus muscles.

History of present illness

The period from the onset of symptoms to the time of admission to our hospital ranged between 5 and 20 d (mean 8.4 d). Two of the patients were admitted first to other hospitals, treated there for 7-10 d, then transferred to our institution for additional treatment. All patients had undertaken home treatment, including nonspecific antivirals, vitamins, antipyretics, and antibiotics. In addition, 2 were taking oral steroids, 5 were taking antiplatelet drugs (*e.g.*, acetylsalicylic acid, dipyridamole,

Table 2 Characteristics of the reported cases

Characteristic	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Age in yr	86	74	65	72	74
Sex	Male	Male	Male	Male	Male
Comorbidities	AH, IHD, PE, AF, PM, CKD	AH, IHD, AF	AH	AH, asthma	AH, IHD, diabetes mellitus, AF
Chronic anticoagulant/antiplatelet use	Acenocoumarol	Acenocoumarol	No	Rivaroxaban	Rivaroxaban
Clinical presentationat admission	Fever, asthenia, loss of appetite	Fever, asthenia	Fever, asthenia	Fever, cough	Fever, asthenia, cough, dyspnea
Duration of illness before admission (days)	4	7	7	12	7
SpO_2 at admission (%)	88	80	75	70	90
Time from admission to bleeding (days)	10	19	12	10	11
Type of bleed	RSH, extraperitoneal	SRH	SRH	SRH	SRH and RSH
Signs and symptoms of bleed	Abdominal, back pain	Abdominal pain, low hemoglobin	Abdominal, back pain	Abdominal pain	Low hemoglobin, abdominal pain, asthenia, swelling (right)
Hemodynamic instability	No	Yes	No	Yes	No
Maximum O_2 therapy prior to bleed	7 L, mask	CPAP 85%	15 L, mask	15 L, mask	12 L, mask
Pulmonary changes	Moderate	Severe	Severe	Moderate	Severe
Length of hospitalization (days)	17	31	20	10	18
Anticoagulation (prophylactic)	No	No	No	No	No
Anticoagulation therapeutic	LMWH 6000 IU, BID; Acenocumarol	ivHEP, LMWH 6000 IU, BID	LMWH 6000 IU, BID	ivHEP	ivHEP
Antiplatelet therapy	No	ASA, clopidogrel	ASA	ASA	ASA
Steroids	Methyl-prednisolone	Methyl-prednisolone	Methyl-prednisolone	Methyl-prednisolone	Methyl-prednisolone
Bioproduct units (pRBC/FFP)	None	5/6	0/2	No	4/2
Surgery	Yes	Yes (x 2)	No	No	Yes
Outcome	Discharged	Died	Discharged	Died	Discharged

AH: Arterial hypertension; IHD: Ischemic heart disease; AF: Atrial fibrillation; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; PE: Pulmonary embolism; PM: Pace maker; ASA: Acetylsalicylic acid; RSH: Rectus sheath hematoma; SRH: Spontaneous retroperitoneal hematoma; OTI: Orotracheal intubation; CPAP: Continuous positive airway pressure; ivHEP: Intravenous heparin; LMWH: Low molecular weight heparin; IU: International unit; BID: Twice daily; pRBC: Packed red blood cells; FFP: Fresh frozen plasma.

nattokinase), 4 were on chronic anticoagulation for either history of atrial fibrillation or pulmonary embolism (2 on acenocoumarol and 2 on rivaroxaban).

On the day of hospitalization, all patients underwent plain chest CT and were diagnosed with bilateral pneumonia, except for 1 patient with unilateral lung involvement. The typical morphological changes (ground-glass opacities, "crazy-paving" pattern, interlobar septal thickening, dilated pulmonary vessels, *etc*) were present in all patients. Two had more chronic changes on CT (*e.g.*, coarse consolidation of the parenchyma, fibrotic changes), as a more extended period had passed from the onset of symptoms.

Regarding severity, 2 patients had mild involvement of the lung parenchyma, 5 had moderate involvement, and 4 had more severe changes. During the clinical course of the viral disease, oxygen (O_2) needs varied. The maximum O_2 therapy prior to bleeding ranged from 5-7 L/min by mask or nasal cannula in 4 patients, 9-15 L/min reservoir mask in 5 patients, 1 patient requiring a continuous positive airway pressure mask with 85% O_2, and 1 patient requiring mechanical ventilation.

History of past illness

All 11 patients had ongoing arterial hypertension. In addition, 4 patients had ischemic heart disease, 3 had atrial fibrillation and chronic kidney disease, 2 had asthma, and 1 had chronic obstructive pulmonary disease and diabetes.

One of the patients had a history of renal transplant recipient (14 years ago) and had undergone abdominal surgery for a mesenteric tumor. Another patient had acute pulmonary embolism 2 wk before hospitalization, which was managed with local fibrinolysis. This same patient also had implantation of a pacemaker type dual chamber system for trifascicular block (3 years ago), left ventricular dysfunction, and pulmonary arterial hypertension. One patient had undergone surgery for thyroid cancer (1 year ago). Another patient had a recent ischemic stroke (8 mo ago) and recent radiation for treatment of squamous cell carcinoma of the left tonsil. One had a history of tuberculosis, and another had a history of 2 ischemic strokes. One of the patients with ischemic heart disease underwent stent implantation of the right coronary artery after a myocardial infarction (8 years ago). None of the patients had chronic liver disease or a history of major bleeding. This was a particularly important factor to be excluded to prevent confounding by other liver disease or other coagulopathy unrelated to COVID-19.

Personal and family history

No patient had a family history of liver disease, bleeding disorder, or other coagulopathy.

Physical examination

On physical examination at admission, varying signs of viral infection and bilateral pneumonia were observed in all patients, except for 1 with only unilateral (left) lung involvement. The measured initial oxygen saturation (SpO_2) on room air ranged between 70% and 97%.

At the onset of symptoms that led to bleeding complications being considered, the most common finding was abdominal pain, the location of which depended on the site of bleeding. Four patients with RSH had visible swelling in the region of the affected rectus muscle, which was painful upon palpation. One had abdominal rigidity with guarding. Three of the patients had hemodynamic instability with low blood pressure and tachycardia accompanied by impaired respiratory function.

Laboratory examinations

All patients underwent routine laboratory testing. Serum inflammatory and hematological markers found at admission are shown in Table 3. Of note, 10 patients had low hemoglobin (between 11 g/L and 52 g/L) (Figure 1).

Imaging examinations

For all patients, multidetector computed tomography (MDCT) images were reviewed for the presence of extravasated contrast material, a CT finding indicative of active hemorrhage. Imaging studies were performed on a Philips Brilliance CT 256-slice scanner, and images and reconstructions were analyzed on an ISP workstation.

Active bleeding was identified in 6 patients out of 11 with a total of 14 identified sites of bleeding (7 intra- or retroperitoneal and 7 extraperitoneal locations). Five of these patients received immediate surgical treatment. One patient with chest wall hematoma underwent angiographic intervention 2 h after MDCT, which confirmed the imaging findings (Figures 2-12).

Despite the typical intraabdominal and retroperitoneal locations of hematomas, we also observed some uncommon sites of anticoagulant-related hematomas, such as the gluteal region and the chest wall (Figures 13-15).

MULTIDISCIPLINARY EXPERT CONSULTATION

Each patient was discussed on an interdisciplinary council board, which included a pulmonologist, an abdominal surgeon, a radiologist, and an intensive care specialist. The decision for a conservative or surgical approach was made after detailed assessment of the risk factors and outcomes for both treatment strategies.

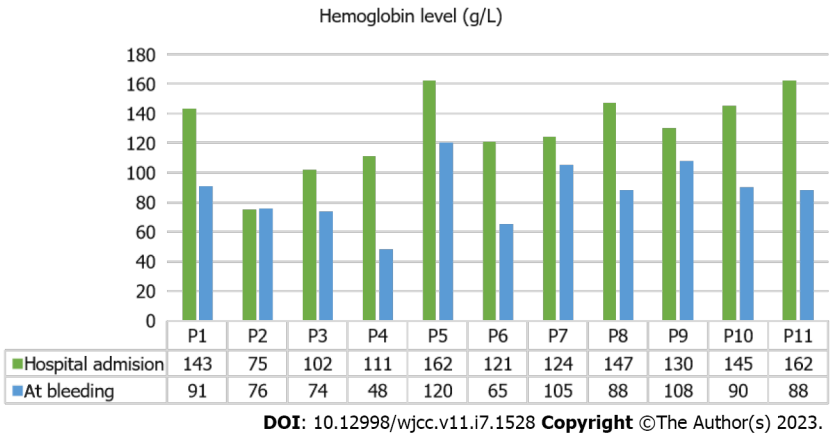
FINAL DIAGNOSIS

Based on clinical and laboratory findings together with the imaging studies, all patients were diagnosed with SRH, RSH, or other abdominal bleeding or hematoma.

Table 3 Inflammatory markers in the current case series

Marker	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
At admission											
Hgb in g/L	143	75	102	111	162	121	124	147	130	145	162
PLT as 10^9/L	197	262	179	254	325	198	354	80	178	131	103
Ly as 10^9/L	0.74	0.83	0.58	0.49	1.1	0.66	0.75	0.47	0.64	0.21	0.57
Cr in μmol/L	124	224	53	72	48	55	71	60	72	57	140
LDH in μ/L	330	451	154	230	502	405	241	491	638	360	760
Ferritin in ng/mL	238.8	535	1027	198.9	> 1675.5	939	1635	> 1675.5	> 1675.5	632	> 1675.5
D-dimer in μg/mL	0.68	1.1	0.30	0.98	1.57	1.07	1.55	1.95	2.03	0.61	0.77
CRP in mg/L	65.6	108	3.1	13	20.4	57.7	7.5	6.4	113.9	1.0	72.5
INR	1.0	1.1	1.07	1.07	1.02	1.0	1.1	1.09	1.01	1.1	1.33
At bleeding											
Hgb in g/L	91	76	74	48	120	65	105	88	108	90	88
PLT as 10^9/L	271	151	206	93	200	279	245	57	222	129	149
Ly as 10^9/L	1.2	0.55	0.59	1.7	1.4	0.94	0.89	0.37	0.55	0.37	0.28
Cr in μmol/L	71	251	46	92	48	56	130	43	55	80	96
LDH in μ/L	335	437	155	335	441	717	311	503	521	719	405
Ferritin in ng/mL	597	243	889	166.3	720	689	971	> 1675.5	906	437	1292
D-dimer in μg/mL	5.46	1.7	0.27	2.7	2.2	1.22	2.36	1.63	2.5	0.61	0.99
CRP in mg/L	8.6	31	2.8	179.5	80.5	160	76.3	87	22.1	5.8	14.7
INR	1.0	1.0	1.05	3.5	1.04	1.0	2.5	1.1	1.06	3.6	1.51

LDH: Lactate dehydrogenase; INR: International normalized ratio; CRP: C-reactive protein; Hgb: Hemoglobin; Ly: Lymphocytes, Cr: Creatinine; PLT: Platelets.



DOI: 10.12998/wjcc.v11.i7.1528

Figure 1 Dynamics of hemoglobin concentration in coronavirus disease 2019 patients.

TREATMENT

Per our hospital's guidelines, all patients received standardized COVID-19 treatments. Oxygen therapy, remdesivir, intravenous corticosteroids, proton pump inhibitors, bromhexine, antipyretics, and anticoagulants were all part of the treatment. The standard treatment protocol was applied to all patients. It included O_2 therapy with changing amounts depending on the needs and the clinical course; anticoagu-

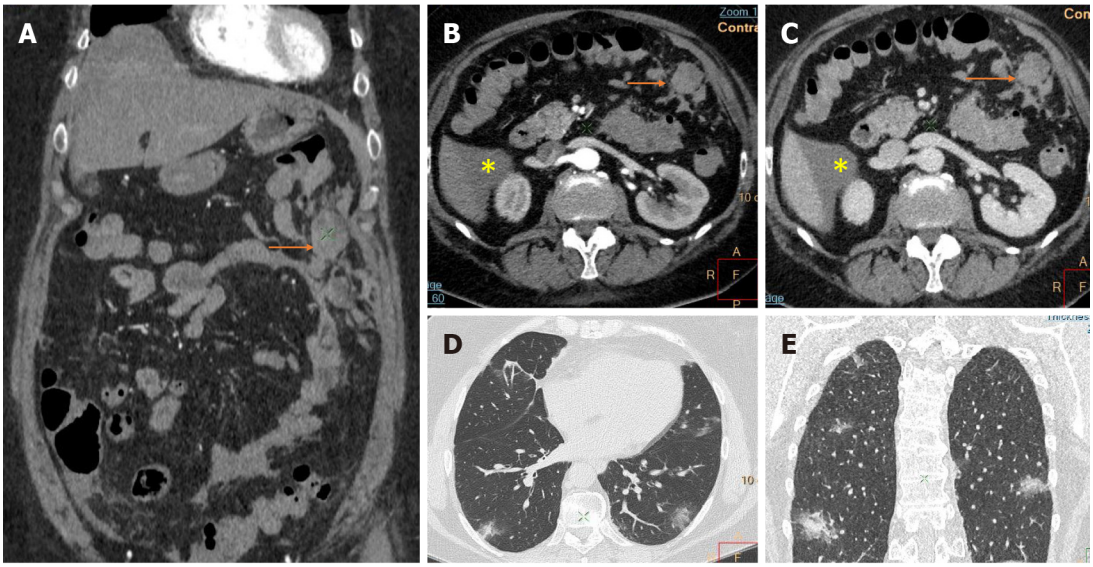


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Figure 2 Computed tomography images of intraabdominal hemorrhage and lung involvement by coronavirus disease 2019 pneumonia. A: Coronal reconstruction; B and C: Axial images with contrast demonstrate an intraabdominal hemorrhagic collection in the left upper quadrant without clear visualization of the site of bleeding (arrows) and small ascites close to the lower pole of the liver (asterisk); D and E: Bilateral lung "ground glass" consolidations in coronavirus disease 2019 pneumonia.

lation either with subcutaneous low molecular weight heparin (LMWH) or intravenous heparin (ivHEP) (7 patients were treated with therapeutic doses due to concomitant AF, recent PE, or high risk for thrombotic complications). All patients received anticoagulant therapy, either with subcutaneous LMWH or ivHEP. Those with past vascular incidents and in cases following therapeutic procedures, 7 patients were given antiplatelet medication (acetylsalicylic acid) as well. All patients were given intravenous corticosteroids (methylprednisolone in 10 and dexamethasone in 1) in optimal doses depending on the clinical course and oxygen needs. One patient was also treated with remdesivir for 5 d, and another with 2 units of convalescent plasma. According to the antibiogram and clinical data on bacterial infection, antibiotics were used only in patients with positive microbiological tests. All patients received symptomatic medications.

After confirmation of bleeding complications with contrast CT, anticoagulant and antiplatelet therapies were immediately stopped. Five patients underwent surgery for hemostasis and drainage of hematoma, and 6 were treated with conservative methods (*e.g.*, replacement with blood products, blood pressure control, hemostatic medication, *etc*). One patient needed a second surgery due to continuing bleeding and a drop in hemoglobin despite replacement with packed red blood cells (pRBC) and fresh frozen plasma (FFP). In 7 patients (63.7%), blood products were transfused according to laboratory markers of blood loss and hemostatic impairment. Product replacement ranged from 0 to 6 units for pRBC and 2 to 6 units for FFP. Anticoagulation with LMWH in reduced dosage was restored as soon as no signs of active bleeding were observed. Three patients with higher risk of thrombotic complication due to AF or recent PE received LMWH or ivHEP sooner, with monitoring of activated partial thromboplastin time. Supportive measures and early rehabilitation were applied to all patients.

Nonsurgical treatment included tranexamic acid and transfusion of bioproducts such as FFP and pRBC. Based on laboratory data, almost two-thirds of our patients received transfusions with varying volumes of these blood products (pRBC and FFP). However, due to low hemoglobin level and clinical signs of ongoing bleeding, only one patient required subsequent surgical treatment. After the second intervention, there was no evidence of active bleeding in the first 24-48 hours, and preventative anticoagulant medication was restarted.

OUTCOME AND FOLLOW-UP

Four of 11 patients died, resulting in a 36.3% mortality rate among patients with the complication of abdominal bleeding. Three of the 4 fatal cases did not undergo surgery, and 1 surgery was revised due to continuous bleeding. Half of the death cases were in patients with RSH, and the other half were in the SRH group. Two of the patients died the same day as the complication of bleeding complication was found, and the deaths were attributed to the hemorrhage in the background of persistent and worsening pulmonary infection. The other 2 patients died following the progression of the viral disease and associated respiratory failure. Hospital stays ranged from 10 to 31 d (mean 17.9 d; mean 15.5 d for those

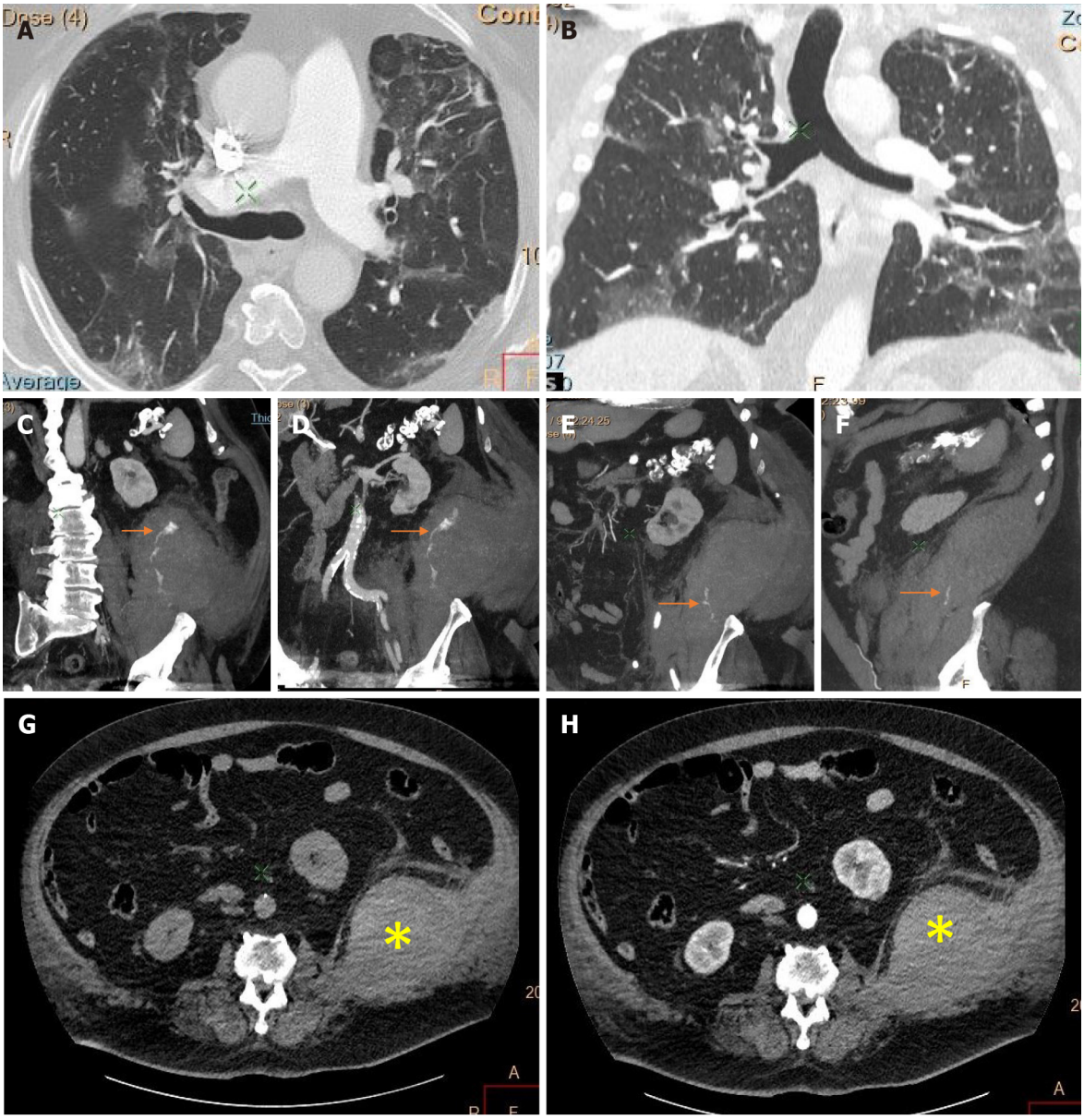

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Figure 3 Thoracic and abdominal computed tomography of a large retroperitoneal hematoma. A: Bilateral lung involvement with coronavirus disease 2019 (COVID-19) pneumonia in cross section; and B: In vertical section; C-F: Multiplanar reconstructions present the site of active bleeding and the jet from the extravasated contrast material (arrows); C-H: The hematoma arises from the internal, the external oblique, and the transverse abdominal muscles and invades the adjacent psoas, quadratus lumborum, and iliacus muscles on the left, which appear thickened (asterisk).

who died and mean 19.2 d for discharged patients). Of the patients who were discharged, 1 developed the complication of delayed wound healing with surgical site infection and infection of the hematoma, which led to a second admission and surgical revision of the wound with lavage and continuous drainage.

DISCUSSION

Since the beginning of the COVID-19 pandemic, many reports have shown that SARS-CoV-2 is linked with various thrombotic events[31]. Therefore, the putative culprit was thought to be COVID-19-induced coagulopathy, in which micro- and macrovascular thrombosis may occur (*e.g.*, deep venous thrombosis, pulmonary intravascular coagulation, pulmonary embolism)[32,33]. As a result, anticoagulant treatments are often administered to these patients, as suggested by worldwide recommendations[34]. The mortality rate of these complications in COVID-19 units is significant, and it has been reported to surpass 50%[35,36].

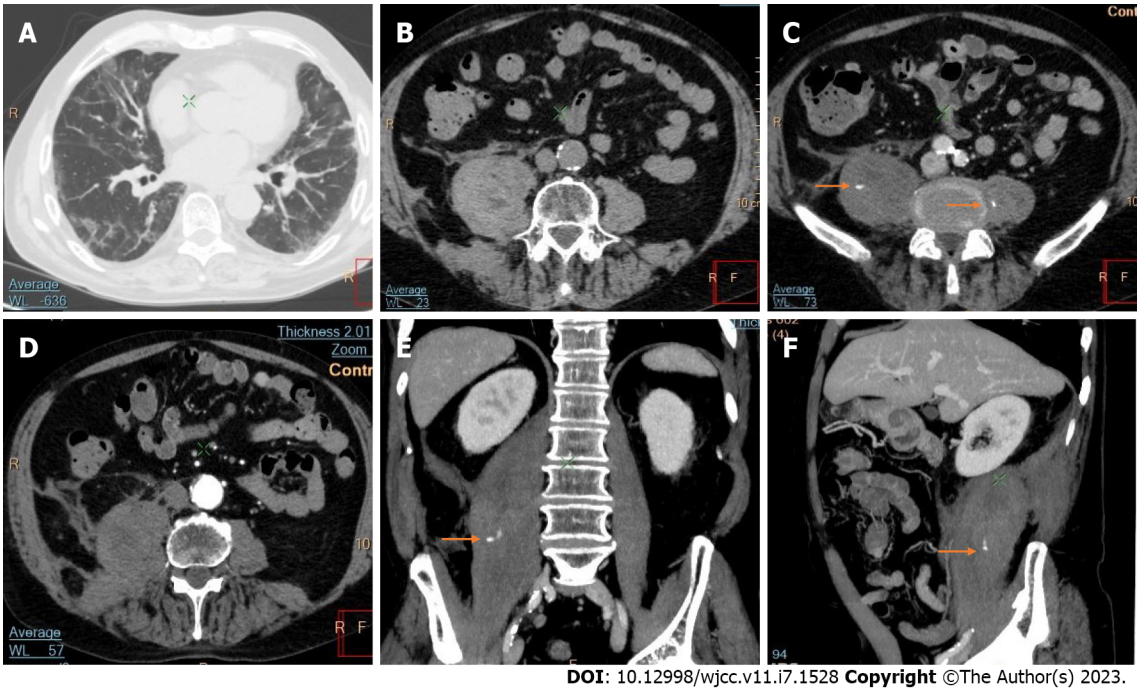

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Figure 4 Axial computed tomography followed by coronal and sagittal reconstructions of retroperitoneal hematoma. A: Axial computed tomography of inflammatory consolidations in bilateral coronavirus disease 2019 pneumonia; B-F: The hematoma originates from psoas major (B and C), the right quadratus lumborum (D), and iliacus muscles (E and F); C, E and F: Extravasated contrast material points to the site of active bleeding in the right psoas muscle (arrows).

Our study presents 11 cases of spontaneous retroperitoneal and abdominal bleeding in hospitalized, anticoagulated COVID-19 patients at our institution (Tables 1 and 2). The average age of our patients was 74.27 ± 11.75-years-old, and there was a male predominance (87.5%). The signs of bleeding appeared 9.45 ± 4.34 d after hospital admission. Abdominal pain was the most common clinical complaint among our group (90%), followed by back pain and leg edema. Ten patients had significant hemoglobin level reductions (> 20 g/L), while only 1 showed no changes in blood count analyses (Figure 1). Seven patients also received antiplatelet therapy with ASA due to previous arterial interventions or incidents such as ischemic heart disease with myocardial infarction or ischemic stroke.

Yeoh *et al*[37] demonstrated that the diagnosis of retroperitoneal hematoma requires a high level of clinical suspicion, since patients often do not develop clinically visible signs and symptoms until significant blood loss has already occurred. These individuals are at substantial risk of bleeding due to strong anticoagulant dosages, commonly combined with low platelet counts. The authors advise suspecting bleeding in patients with considerable groin, flank, stomach, or back discomfort following an interventional procedure and in the setting of anticoagulation[37].

We performed CE-CT on all patients presented. Active bleeding was identified in 6 of 11 patients, with a total of 14 bleeding sites (7 intra- or retroperitoneal and 7 extraperitoneal locations) (Figures 2-12). With respect to anticoagulation therapy, 9 of 11 patients were on LMWH, while only 2 patients received ivHEP before the bleeding occurred. Aspirin was also administered to 63.3% of patients (Tables 1 and 2). We discontinued the anticoagulation therapy as soon as the bleeding was established. Seven of 11 patients described were conservatively managed with fluid resuscitation, while the other 5 were surgically treated.

Following the identification of bleeding by CE-CT, anticoagulant and antiplatelet medications were immediately discontinued. Once bleeding sources were identified, we stratified the patients into two groups: Patients with stable hemodynamic parameters and patients with hemodynamic instability. In patients with stable hemodynamic parameters (54.55%), conservative therapy was applied, whereas the remaining 5 patients underwent surgical drainage, hemostasis, and drain placement. The average hospital stay was 17.90 ± 6.46 d, and the mortality rate was 36.36% (Tables 1 and 2).

This case series aims to raise awareness in clinicians of the complication of bleeding in COVID-19 patients, with particular emphasis on the necessary vigilant observation of anticoagulated COVID-19 patients. However, despite being an uncommon complication, COVID-19- related bleeding still carries a significant mortality rate. Accordingly, clinicians must look for nonspecific signs of bleeding in this group, including abdominal or flank pain, and signs of hypovolemia or anemia to ensure early and efficient treatment[38]. To this end, anticoagulation therapy has been included in treatment guidelines [39,40].

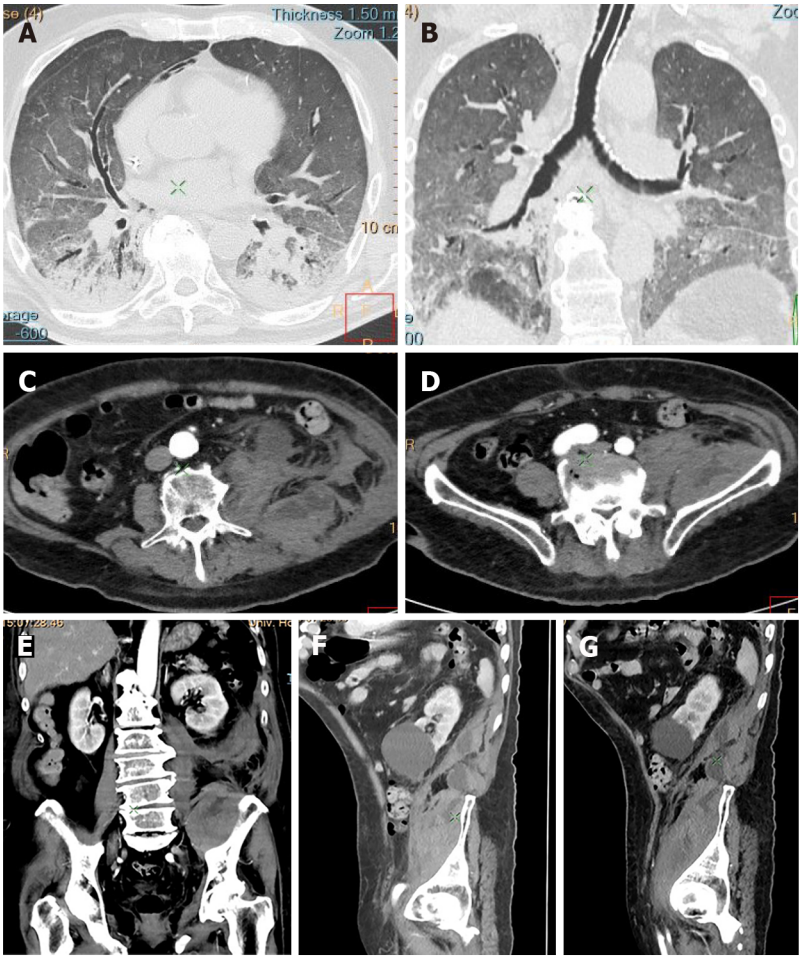

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Figure 5 Abdominal and pelvic computed tomography and dynamic contrast enhanced computed tomography of retroperitoneal hemorrhage on the left. A: Bilateral lung consolidations with posterior predilection, predominantly involving the lower lobes, including "ground glass" opacities and vascular enlargement in cross section; B: Bilateral lung consolidations with posterior predilection, predominantly involving the lower lobes, including "ground glass" opacities and vascular enlargement in vertical section; C-E: Retroperitoneal hemorrhagic collection in the left flank and iliac fossa by postcontrast computed tomography axial and coronal images. Axial and coronal reformat images of dilatation of the psoas muscles; F and G: Sagittal reconstruction plane of the entire length of the iliac muscle affected by a hematoma.

However, taking into consideration their side effects, there has been substantial discussion regarding whether anticoagulant therapy should be applied in particular conditions and at what dosage[39,41]. A plethora of retrospective studies have indicated that patients receiving anticoagulation in therapeutic doses had significantly higher risks of bleeding and inpatient mortality[24,27,42,43], which was also corroborated in our study[44-48]. However, the impact of anticoagulation on bleeding in hospitalized COVID-19 patients is currently being studied. In a study conducted by Musoke *et al*[49], COVID-19 patients receiving therapeutic anticoagulation had significantly higher rates of major bleeding than those not receiving anticoagulation. In contrast, subtherapeutic and prophylactic doses had no significant differences in primary bleeding outcomes compared to patients not receiving anticoagulation. Despite the danger of bleeding, anticoagulation has been proven to improve survival in individuals with severe COVID-19 infection[49].

It is thought that microvascular susceptibility caused by atherosclerosis, COVID-19 induced microtrauma, and mechanical disturbance (*e.g.*, cough) might contribute to retroperitoneal bleeding. However, more studies must be conducted to elucidate the exact pathophysiological mechanism[50-52].

CT is a proven technique for evaluating and detecting hemorrhagic lesions. Intravenous contrast material administration is needed to visualize the precise location and site of bleeding and identify the affected vessels. Active bleeding can be seen as a focal jet of extravasated contrast material on multidetector CT images. Maximum Intensity Projection (MIP) and Volume Rendering (VR) techniques are valuable tools for the presentation of various findings of CT angiography. These tools are suited to display even small vessels and facilitate the visualization of any bleeding site. Active hemorrhage can be demonstrated best in the arterial phase, and may involve the peritoneal cavity, the mesentery, or the retroperitoneum. Less common locations of bleeding following anticoagulant therapy in patients with mild or severe COVID-19 infection include the chest wall and various muscles (*e.g.*, gluteus muscles).

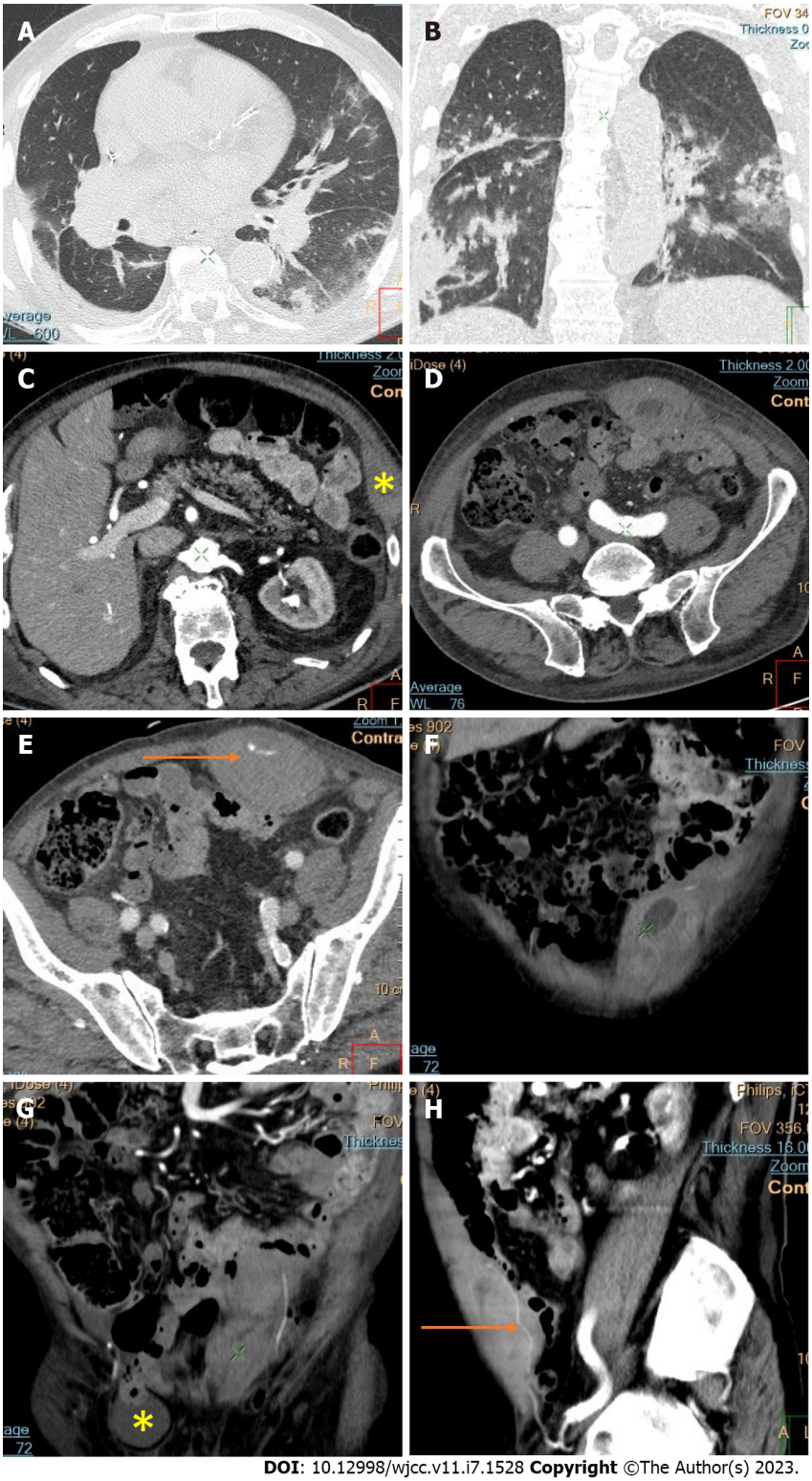

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Figure 6 Computed tomography of active bleeding hematoma in the left rectus abdominis muscle. A: Pulmonary "ground glass" opacification and interstitial thickening due to coronavirus disease 2019 (COVID-19) pneumonia in cross section; B: Pulmonary "ground glass" opacification and interstitial thickening due to COVID-19 pneumonia in vertical section; C: Hematoma between the internal and external abdominal muscles on the left (asterisk); D-H: The exact site of bleeding from the inferior epigastric artery on axial post-contrast images and coronal and sagittal maximum intensity projection reconstructions (arrows); G: Right-sided inguinal herniation containing a small bowel segment as an additional finding (asterisk).

Furthermore, there is no confirmed pathognomonic sign to suggest retroperitoneal hemorrhage, especially in the scenario of overt bleeding without significant hemoglobin level changes. Thus, a high level of clinical suspicion is required to identify nonspecific symptoms such as groin, abdominal, back, or lower extremity discomfort[38,43].

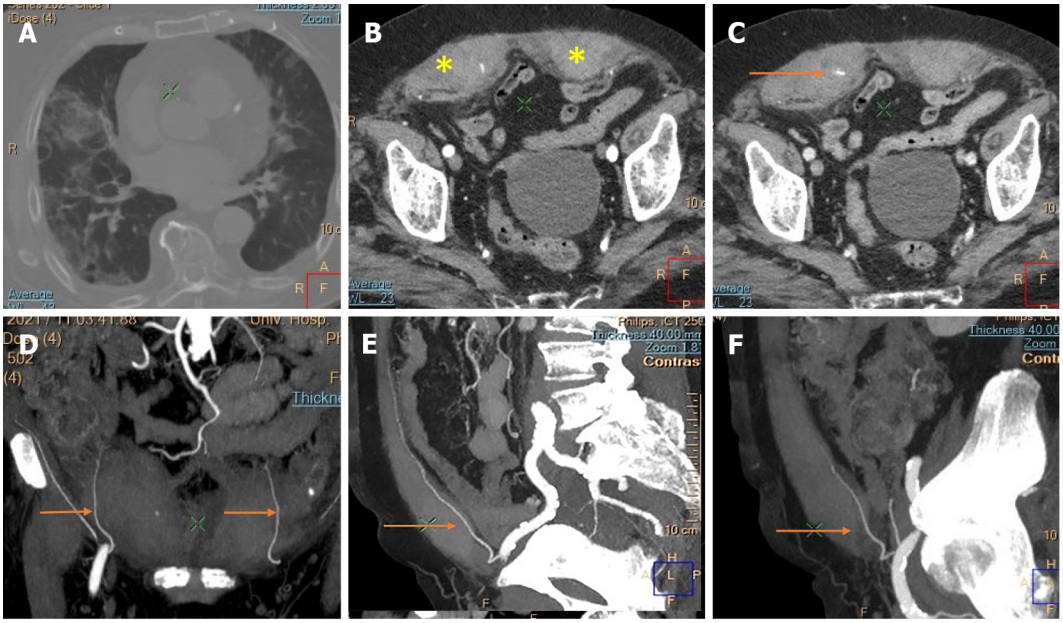

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Figure 7 Axial computed tomography with maximum intensity projection reconstructions show bilateral hematomas of the right abdominal muscles. A: Bilateral "ground glass" opacities in the context of coronavirus disease 2019 pneumonia; B and C: Post-contrast axial images; D-F: coronal and sagittal reconstructions demonstrate both hematomas (asterisks) and active bleeding from branches of the inferior epigastric artery (arrows).

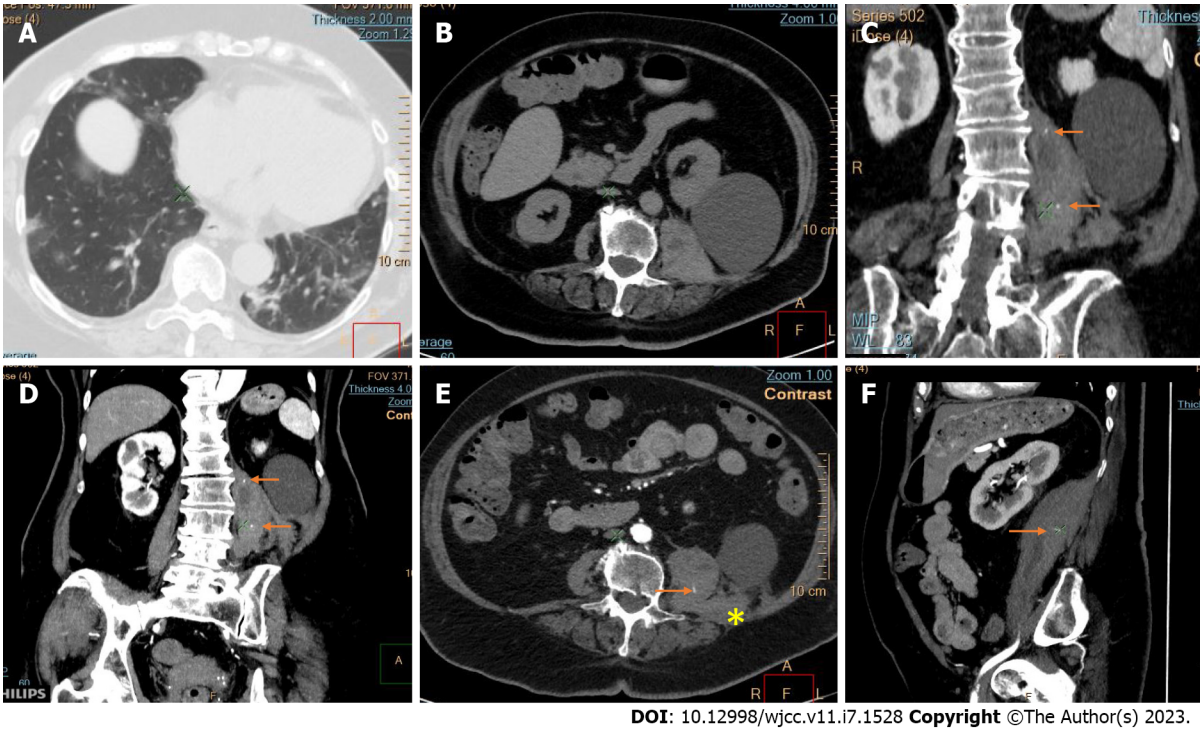

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Figure 8 Abdominal pre- and post-contrast images and thoracic computed tomography in a patient with coronavirus disease 2019 and hematoma of the left psoas muscle. A: "Crazy caving" pattern and linear interstitial thickening in the basal lung segments in organizing coronavirus disease 2019 pneumonia; B-F: A large hematoma of the left psoas muscle with infiltration of quadratus lumborum (asterisk); B-E: Large simple cortical cyst of the left kidney; C-F: Active bleeding from lumbar branches of the iliolumbar artery is indicated on post-contrast computed tomography images (arrows).

Regarding diagnostic management, CE-CT is considered the best imaging technique for evaluating and detecting hemorrhagic lesions. Intravenous contrast material administration is necessary to visualize the precise location and site of bleeding and identify the affected vessels. Active bleeding can be seen as a focal jet of extravasated contrast material on multidetector CE-CT images. MIP and VR techniques are valuable tools for the presentation of various findings of CT angiography. These tools are suited to display even small vessels and facilitate visualization of any bleeding site. Active hemorrhage

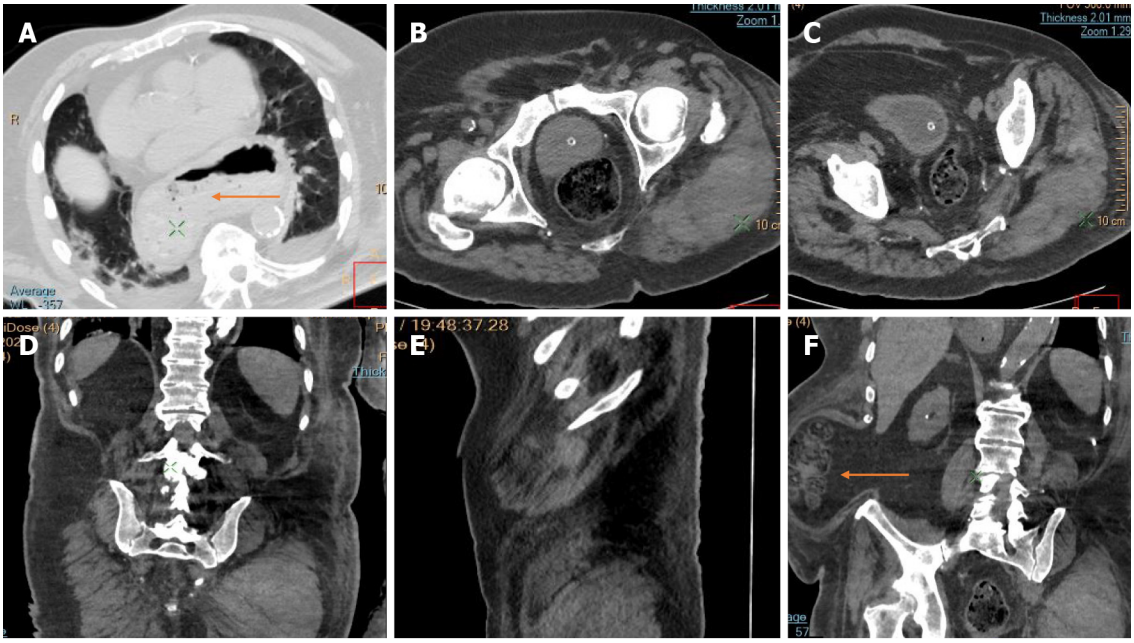

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Figure 9 Large hematoma of the left gluteus maximus muscle in coronavirus disease 2019 pneumonia. A: Lung parenchymal involvement by coronavirus disease 2019 pneumonia; B-F: Native computed tomography axial images and coronal and sagittal maximum intensity projection reconstructions visualize an unusual localization of anticoagulant-related muscular hematoma; F: Giant hiatal hernia and right lateral abdominal wall herniation (arrows) as additional findings.

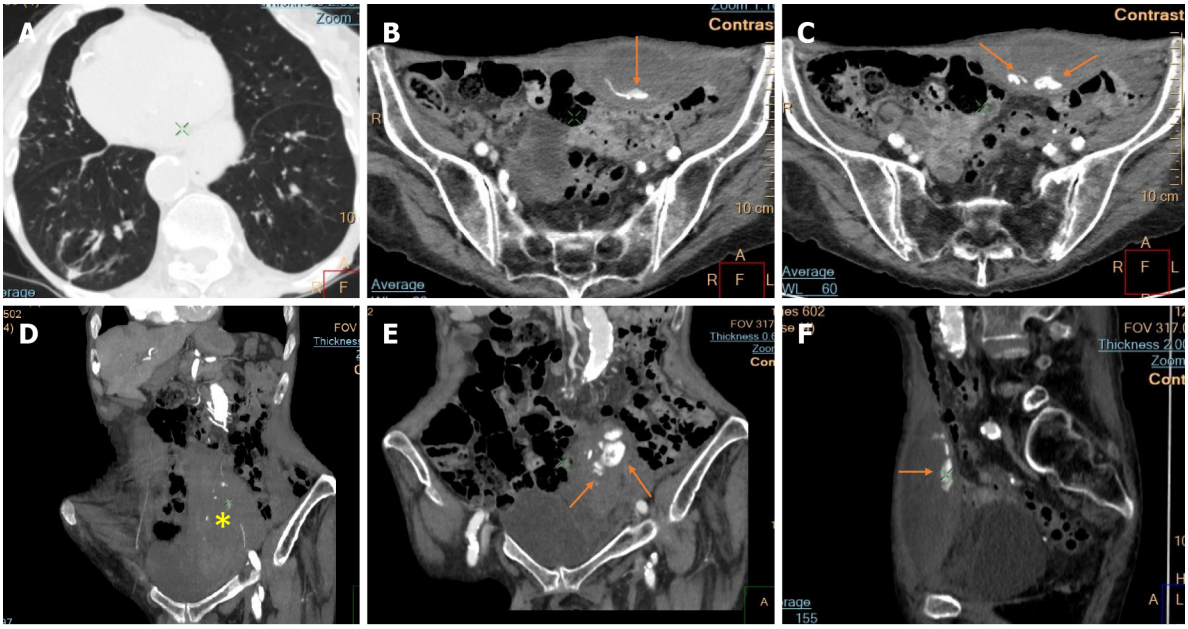

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Figure 10 Postcontrast computed tomography of a massive hematoma of the anterior abdominal wall. A: This patient was recovering from coronavirus disease 2019 pneumonia with some residual post-inflammatory basal consolidations of the right lung; B-E: Depot of extravasated contrast is seen in the left rectus abdominis muscle (arrows); F: Clear bleeding from the left inferior epigastric artery (asterisk).

can be demonstrated best in the arterial phase and may involve the peritoneal cavity, the mesentery, or the retroperitoneum[53,54].

Early diagnosis and prompt management of abdominal bleeding are paramount to prevent hematoma expansion and compression of surrounding tissues[54]. According to the available reports, there is no clear consensus on the best therapeutic strategy for retroperitoneal bleeding in COVID-19 patients[54]. However, the prevailing primary treatment consists of discontinuing anticoagulant medication as soon as possible and replacing lost volume with fluids and bioproduct transfusion (pRBC/FFP). Small hematomas and hemodynamically stable patients are managed conservatively[55].

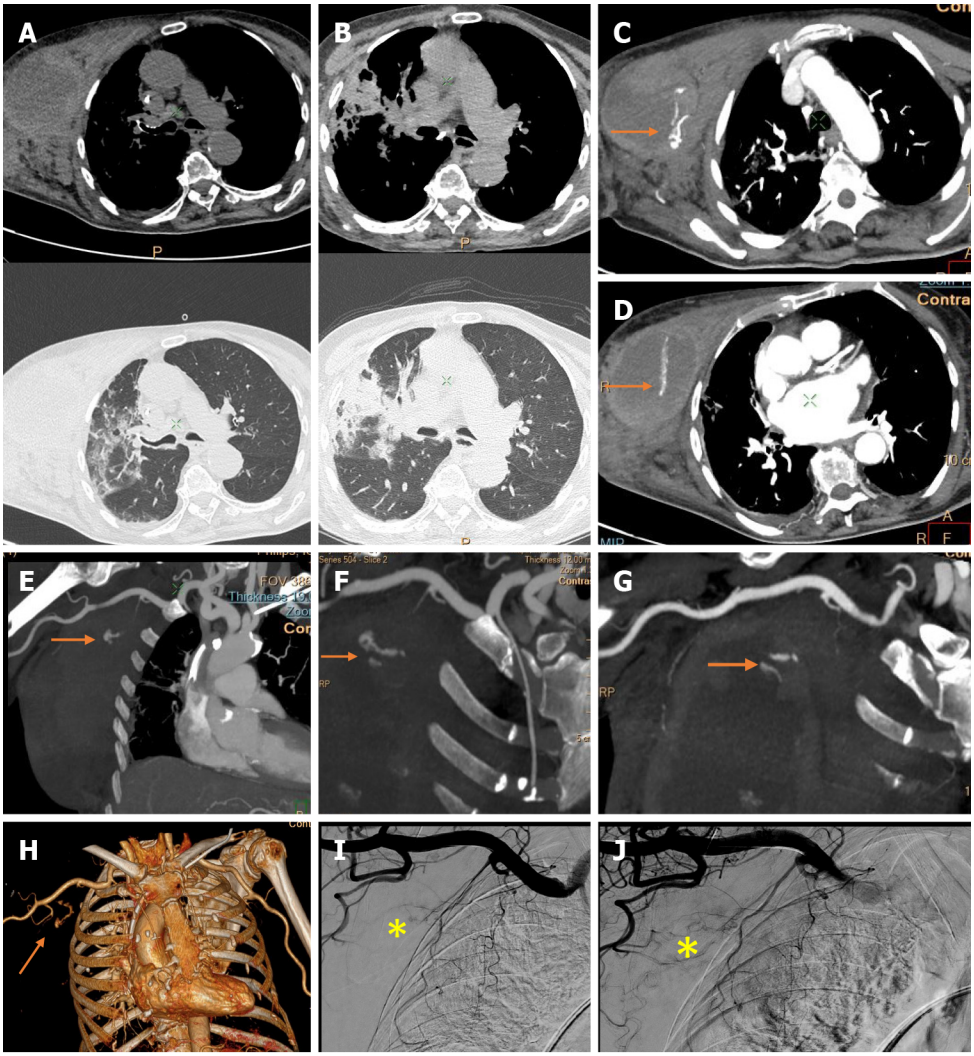

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Figure 11 Computed tomography angiography and digital subtraction angiography of a giant right-sided chest wall hematoma in a patient with coronavirus disease 2019 pneumonia. A-D: Hematoma arising from and infiltrating between the pectoral muscles, with "crazy paving" interstitial inflammatory changes in the right lung; C and D: Post-contrast axial images and coronal reconstructions with two pooling sites of extravasated contrast material within the hematoma (arrows); E-G: Computed tomography angiography maximum intensity projection images; H: Volume rendering three-dimensional reconstructions enable the visualization of a jet from the bleeding vessels (terminal branches of the superior and lateral thoracic artery (arrows). No bleeding from the pectoral branch of the thoracoacromial artery is evident; I and J: Digital subtraction angiograms confirm the predefined sites of bleeding without need of embolization due to bleeding reduction by the compression of those small vessels by the giant hematoma (asterisk).

On the other hand, patients with significant bleeding and hemodynamic instability should undergo arterial embolization or surgical treatment with the goal of increasing survival[55-57].

Our case series has some limitations. Firstly, the number of cases is relatively few, however, our manuscript has gathered the most notable cases of retroperitoneal and abdominal bleeding in anticoagulated COVID-19 patients seen in our institution. Secondly, we are unable to provide follow-up data after patients were discharged. We collected examples of both common and rare cases that illustrate that imaging methods such as CE-CT can be potent tools in the diagnosis and management of bleeding complications in COVID-19 patients. What remains unresolved is how to choose the ideal time for specialized image testing and when to suspect retroperitoneal bleeding in anticoagulated COVID-19 patients; these issues represent fertile topics for future research.

CONCLUSION

It is thought that microvascular susceptibility caused by atherosclerosis, viral-induced microtrauma, and mechanical disturbance (*e.g.*, cough) may contribute to the development of retroperitoneal bleeding in the setting of COVID-19. However, more studies must be conducted to elucidate the exact pathophysiological mechanism of this serious complication. CT is a proven technique for evaluating and detecting hemorrhagic lesions, where intravenous contrast material administration is needed to

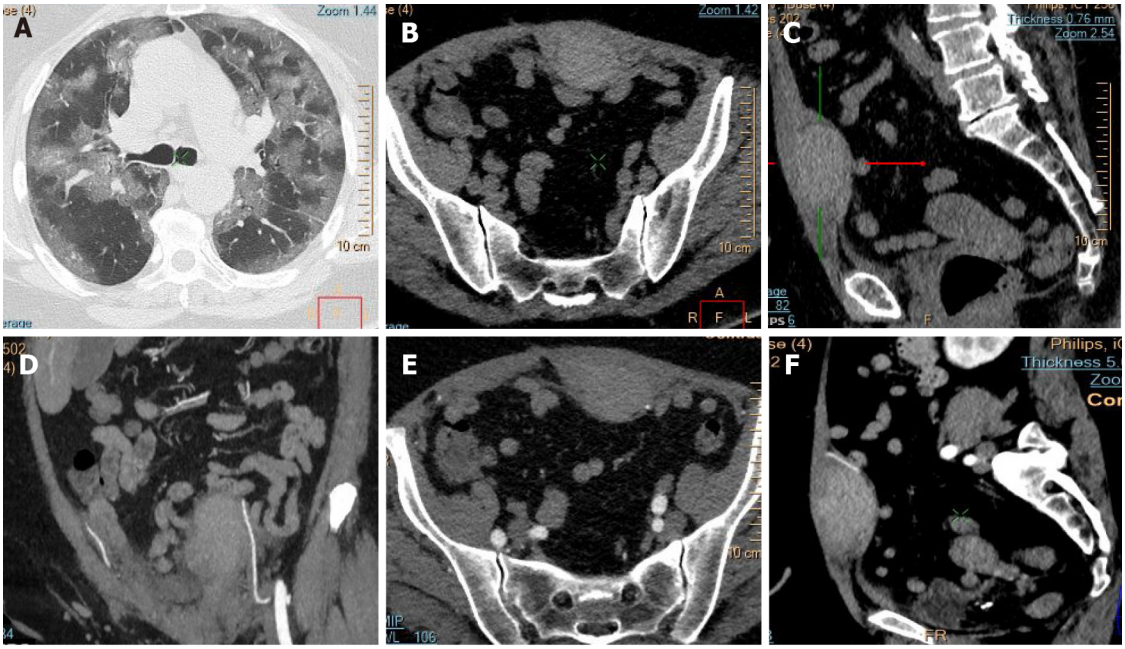

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Figure 12 Thoracic and pelvic computed tomography images of hematoma of the anterior abdominal wall. A: Diffuse "ground glass" opacifications from coronavirus disease 2019 bilateral pneumonia; B and C: Pre-contrast axial and coronal images; D-F: Coronal, axial, and sagittal reconstructions with intravenous contrast show a mild hematoma in the left rectus abdominis muscle due to bleeding from the left inferior epigastric artery.

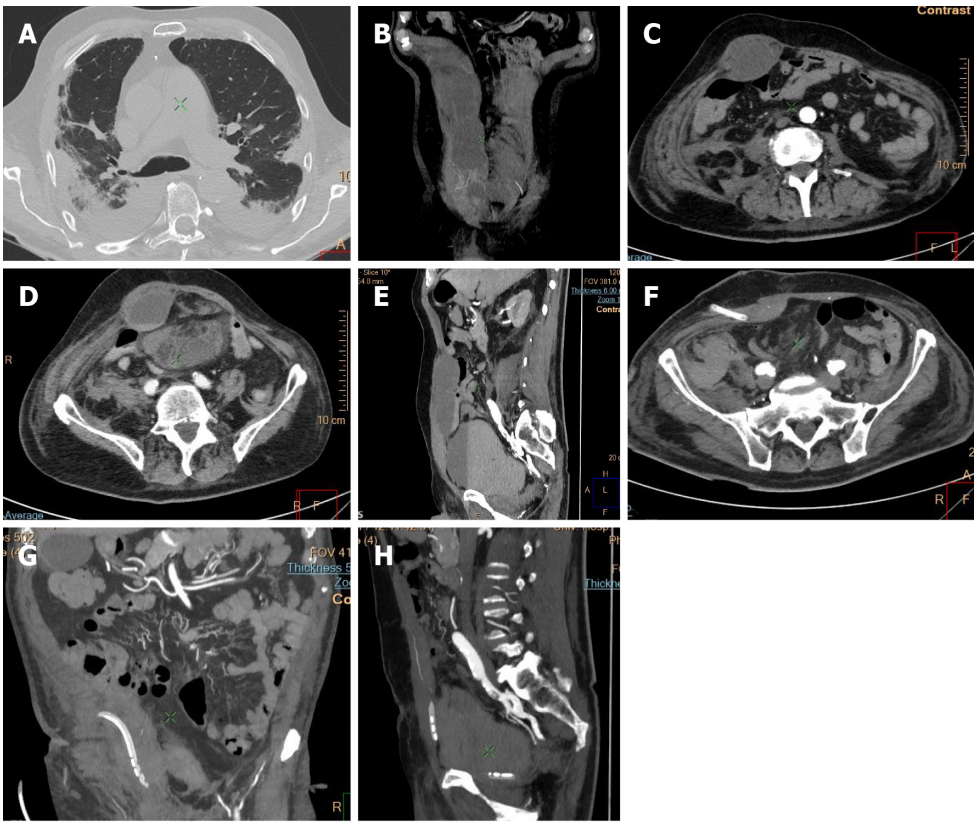

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Figure 13 Axial multidetector computed tomography and maximum intensity projections in coronavirus disease 2019 pneumonia; right retroperitoneal and right abdominal wall hematoma. A: Bilateral pleural effusions and reticular interstitial thickening in organized coronavirus disease 2019 pneumonia; B-E: Nodular thickening of the muscles of the anterior abdominal wall; C, D, F and G: Bloody infiltration of the right iliopsoas and iliacus muscles and posterior renal fascia with probable relationship to the right inferior epigastric artery; F-H: Pelvic drainage of re-bleeding during re-hospitalization.

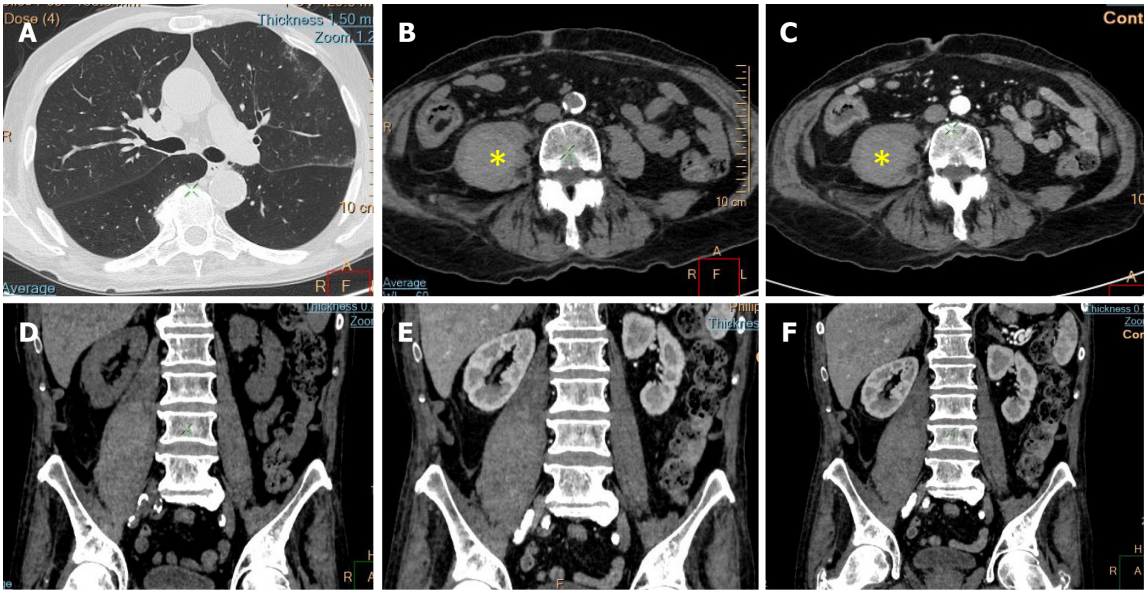

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Figure 14 Computed tomography images of right psoas major hematoma. A: Minor peripheral and subpleural consolidations of the left lung in coronavirus disease 2019 pneumonia; B and C: Axial native and post-contrast images with enlargement of the right psoas muscle (asterisk); D-F: Dilated and hyperdense right psoas muscle by native coronal reconstructions and the same after contrast injection.

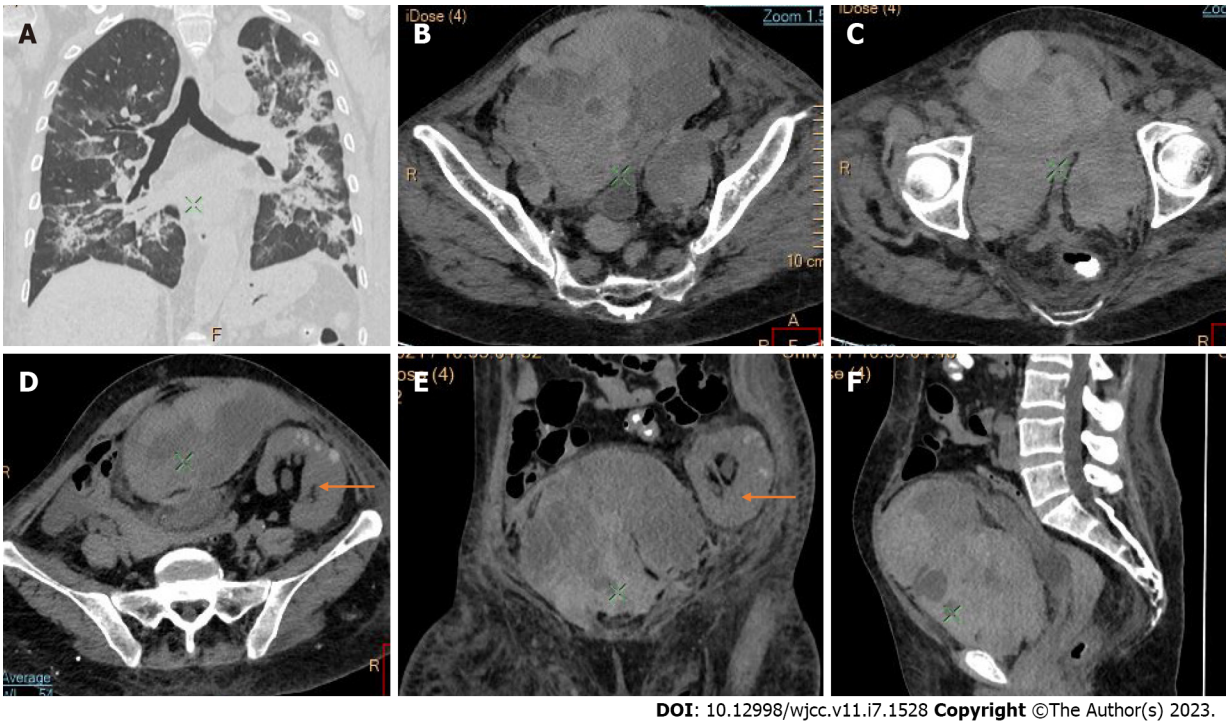

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Figure 15 Computed tomography of enormous pre-peritoneal hematoma with intraabdominal and pelvic localization. A: Severe bilateral consolidations with "crazy paving" due to coronavirus disease 2019 pneumonia; B-D: Axial images; E and F: Coronal reconstructions demonstrate a heterogeneous mass with mixed density; D and E: Transplanted kidney in the left iliac fossa (arrows).

visualize the precise bleeding site and identify affected vessels. Active bleeding can be seen as a focal jet of extravasated contrast material on multidetector CT images. Native and contrast-enhanced MDCT are essential imaging modalities in the diagnosis of hematoma. In addition, MIP and VR techniques with contrast media can help identify the possible site of bleeding. At the same time, digital subtraction angiography may be used to embolize the affected vessels.

Active hemorrhage can be demonstrated best in the arterial phase and may involve the peritoneal cavity, the mesentery, or the retroperitoneum. Less common locations of bleeding following anticoagulant therapy in patients with mild and severe COVID-19 infection include the chest wall and

different muscle groups (*e.g.*, gluteus muscles). However, there is no consensus regarding the best therapeutic strategy for retroperitoneal bleeding in COVID-19 patients. Nevertheless, CE-CT is considered the best imaging technique for evaluating and detecting hemorrhagic lesions in these patients.

FOOTNOTES

Author contributions: Evrev D, Velikova T, and Hadjidekov G conceptualized the study; Evrev D, Sekulovski M, Gulinac M, Dobrev H and Hadjidekov G performed the investigation; Evrev D, Sekulovski M, Gulinac M, Dobrev H and Hadjidekov G provided resources; Evrev D, Sekulovski M, Dobrev H and Hadjidekov G performed the data curation; Evrev D, Dobrev H and Hadjidekov G participated in the data visualization; Evrev D, Sekulovski M, Gulinac M, and Hadjidekov G wrote the original manuscript draft; Velikova T and Hadjidekov G contributed to the writing and reviewed and edited the final manuscript; Velikova T provided study supervision; All authors revised and approved the final version of the manuscript prior to submission.

Informed consent statement: All patients signed informed consent, and the study was conducted following the Declaration of Helsinki and the Ethics norm of the University Hospital "Lozenetz".

Conflict-of-interest statement: All the authors report having no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Bulgaria

ORCID number: Delian Evrev 0000-0001-8092-3195; Metodija Sekulovski 0000-0001-8374-7756; Milena Gulinac 0000-0001-7970-9378; Hristo Dobrev 0000-0002-2723-7425; Tsvetelina Velikova 0000-0002-0593-1272; George Hadjidekov 0000-0001-6917-9887.

S-Editor: Liu GL
L-Editor: Filipodia
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