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Review Article

Acute splanchnic vein thrombosis in patients with COVID-19: A systematic review

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ABSTRACT

There is increasing evidence that coronavirus disease 2019 (COVID-19) is associated with a significant risk of venous thromboembolism. While information are mainly available for deep vein thrombosis of the lower limb and pulmonary embolism, scarce data exist regarding acute splanchnic vein thrombosis (SVT) in this setting. PubMed, EMBASE and Google Scholar English-language articles published up to 30 January 2021 on SVT in COVID-19 were searched. Overall, 21 articles reporting equal number of patients were identified. 15 subjects presented with portal vein thrombosis, 11 with mesenteric vein thrombosis, four with splenic vein thrombosis, and two with Budd-Chiari syndrome. Male sex was prevalent (15 patients), and median age was 43 years (range 26–79 years). Three patients had a history of liver disease, while no subject had known myeloproliferative syndrome. Clinical presentation included mainly gastrointestinal symptoms. Anticoagulation was started in 16 patients. Three patients underwent bowel resection. Ten subjects developed gastric or bowel ischemia, seven of whom underwent bowel resection, and four died after SVT diagnosis.

Although rare, SVT should be seen as a complication of COVID-19. Patients with severe gastrointestinal symptoms should be screened for SVT, as rapid recognition and correct management are essential to improve the outcome of these patients.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is identified as responsible of coronavirus disease 2019 (COVID-19), a clinical condition ranging from mild symptoms, such as impairment of the smell and taste, to the typical pulmonary manifestations including acute respiratory distress syndrome [1]. The virus may also directly damage the intestinal mucosa [2], as gastrointestinal symptoms have been widely reported [3,4]. Furthermore, increasing evidence showed that COVID-19 might be associated with hemostasis impairment, thus predisposing patients to both venous and arterial thromboembolism [5]. While the association between COVID-19 and deep vein thrombosis of the lower limb and pulmonary embolism has been extensively investigated, less is known about thrombotic events in other districts, such as splanchnic vein thrombosis (SVT). SVT is an uncommon manifestation of venous thromboembolism (VTE) that includes portal vein thrombosis (PVT), mesenteric vein thrombosis (MVT), and thrombosis of the liver veins or vena cava inferior (Budd-Chiari syndrome, BCS). SVT is more often diagnosed in patients with cirrhosis or liver malignancy. Other predisposing factors, which are often observed in patients with non-cirrhotic liver, are intra-abdominal surgery, infections and inflammatory diseases, as well as inherited or acquired thrombophilia [6].

Assuming that the splanchnic venous system could be also affected by the COVID-19-related coagulopathy, we conducted a systematic review of current literature on SVT and COVID-19.

2. Methods

We searched in PubMed, EMBASE and Google Scholar English-language articles published between November 2019 and 30th January 2021 including the following MeSH terms “COVID-19 (and related terms 2019 novel coronavirus, SARS-CoV-2 infection, 2019-nCoV infection) and splanchnic vein thrombosis”, “COVID-19 and portal vein thrombosis”, “COVID-19 and mesenteric vein thrombo-

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sis", "COVID-19 and Budd-Chiari syndrome", "COVID-19 and bowel ischemia". Case reports, case series, commentaries, letters to editors, and review articles were considered. We evaluated independently title and abstract for inclusion, double-checking for duplication and extracting the data using the text, tables, and figures of the original published articles. Cross-referencing yielded no additional records and duplicate articles were assessed and subsequently eliminated. All the demographic and clinical characteristics, clinical course and outcomes are reported using median and incidence.

3. Results

Overall, 641 articles were screened, 21 of which were selected according to the above mentioned criteria [7–27]. The included articles were all case reports (except for one case series [10]), and contained description of 21 cases. Overall, 15 patients presented with PVT, 11 with MVT, 4 with splenic vein thrombosis, and 2 with BCS. The clinical features, management and outcome are showed in Tables 1 and 2 and summarized in Fig. 2.

3.1. Comorbidities

Male sex was prevalent (15 patients), and median age was 43 years (range 26–79 years).

Comorbidities included cardiovascular risk factors like obesity (3 patients), type 2 diabetes (2 patients), arterial hypertension and hyperlipidemia (one patient each), as well as asthma (2 patients), Parkinson disease and vascular dementia (one patient each). Three patients had a history of known liver disease (non-alcoholic steatohepatitis (NASH) plus hepatitis B virus (HBV) cirrhosis, chronic hepatitis B, and alcohol-associated cirrhosis). Except for one patient with operated craniopharyngioma, none of the patients had a history of neoplasia or myeloproliferative neoplasms (MPN). In one case, imaging tests performed at admission documented multifocal liver lesions consistent with hepatocellular carcinoma in the setting of newly discovered chronic hepatitis B, whereas no neoplastic thrombus was reported in the patient with known cirrhosis on NASH and HBV on the investigations performed. For ten patients, no comorbidities were reported.

3.2. Presentation

Symptoms and/or signs of SVT were present at COVID-19 onset in ten cases, whereas in seven patients SVT represented a belated manifestation (range 5–21 days). For one subject, SVT was diagnosed as occasional finding with imaging performed in the setting of COVID-19.

Clinical presentation included mainly gastrointestinal symptoms, such as abdominal pain (16 patients), and vomiting (7 patients). Jaundice and diarrhea were reported in one case each. Fever was present for 7 patients, while dyspnea, cough and altered mental status were reported in 4 cases each. One patient had a large volume hematemesis following initiation of heparin for a lower extremity deep vein thrombosis during COVID-19.

3.3. Diagnosis of SVT and of COVID-19

SVT was diagnosed in the outpatient setting in 17 cases. Almost all the diagnosis of SVT required a computed tomography (CT) scan to be confirmed, except in one case (abdominal Doppler ultrasound, DUS). Eight patients displayed multivessel involvement, including upper mesenteric artery for one patient. At the time of SVT diagnosis, features of gastric or bowel ischemia were reported in ten cases.

Diagnostic tests for COVID-19 included real-time reverse transcription polymerase chain reaction (RT-PCR) on nasopharynx swab for 16 patients, confirming COVID-19 in eleven cases, and serological test in 3 cases, all of which were positive. For one subject, SARS-CoV-2 infection was confirmed by immunohistochemistry on a specimen of the resected small bowel, while for two patients the disease was suspected based on clinical features and pulmonary findings at imaging, despite a negative RT-PCR on nasopharynx swab. For 5 patients, the diagnostic test used was not reported by the authors.

Diagnostic workup for inherited or acquired thrombophilia was reported in 11 cases, two of which had positive lupus anticoagulant (LAC) (one at low titer), and one an established diagnosis of essential thrombocythemia (ET). Further tests performed were reported as negative by the authors.

3.4. Treatment and outcomes

Before SVT was diagnosed, three patients were taking anticoagulation therapy (one at therapeutic dose). After the diagnosis, an anticoagulation treatment was started in 16 cases, including unfractionated heparin (UFH) or low molecular weight heparin (LMWH) (11 patients), and Apixaban (2 patients). In three case, the anticoagulant treatment introduced was not specified. Seven patients with radiological features of intestinal ischemia underwent bowel resection, one of whom had also thrombolysis and thrombectomy in the context of upper mesenteric artery thrombosis.

Outcome was available only for 14 patients, four of whom died. These were 2 males and 2 females, aged 79, 62, 61, and 42, respectively. One subject had no known comorbidities, another one had only diabetes reported, the third one had diabetes, obesity, arterial hypertension and cirrhosis, while the last one had extreme obesity and a ventriculoperitoneal shunt due to a partially resected craniopharyngioma. All these patients had multivessel involvement, including upper mesenteric artery, as well as bowel ischemia complicating SVT.

Two subjects had clinical worsening following anticoagulant therapy (one due to subsequent bowel ischemia, and the other one due to tight stenosis of mid-jejunum caused by congenital adhesion band). Both underwent bowel resection and were discharged thereafter. In one case, a 6-week follow-up imaging showed an established PVT with collateralization extending into the upper abdomen. At last, two patients had gastrointestinal bleeding after anticoagulant treatment introduction.

4. Discussion

Venous thromboembolism is a common complication of inpatients with COVID-19, with a prevalence as high as 21% in a recent meta-analysis of over 8 thousand patients [28]. The mechanisms underpinning the strong relationship between SARS-CoV-2 infection and venous and arterial thromboembolism are not clear yet, and likely include endothelial dysfunction, excessive inflammatory response, and hemodynamic components (stasis) [29–33].

There is no specific data regarding SVT, but it can be hypothesized that the above-mentioned mechanisms in patients with predisposing conditions such as chronic liver disease or MPD can lead to a preferential splanchnic location of thrombosis (Fig. 1). Interestingly, however, in a meta-analysis by Diaz et al. on histopathological reports from deceased COVID-19 patients undergoing autopsy or liver biopsy, almost 30% of cases presented hepatic vascular thrombosis in spite of a low prevalence of known chronic liver disease [34].

In the here reviewed cases, male gender was prevalent with a median age of 43 years. Current literature shows that the mean

Table 1
Clinical features of the 21 patients included at the time of SVT diagnosis.

Author	Country	Age, sex	Medical setting on onset	Medical history	Diagnostic test for SARS-CoV-2 infection	Time from COVID-19 to symptoms/signs of SVT	Anticoagulation therapy at the time of SVT diagnosis	Symptoms/signs
De Barry et al. [1]	France	79, F	Outpatient	None	Negative RT-PCR on nasopharynx swab. Suspicion of COVID-19 based on clinical features and pulmonary findings at imaging	Symptoms/signs of SVT at COVID-19 onset	None	Fever, deterioration of general condition, and abdominal pain located in the epigastric area, associated with diarrhea during 8 days
Ignat et al. [2]	France	28, F	Outpatient	None	Not reported	Symptoms/signs of SVT at COVID-19 onset	None	Abdominal pain and vomiting with abdominal guarding at clinical examination
Norsa et al. [3]	Italy	62, M	Outpatient	Obesity, arterial hypertension, T2DM and cirrhosis (NASH + hepatitis B)	Negative RT-PCR on nasopharynx swab. Diagnosis of SARS-CoV-2 infection based on ISH on the resected small bowel (RNAscope technology)	Symptoms/signs of SVT at COVID-19 onset	None	Abdominal pain and bilious vomiting during 3 days, followed by unconsciousness and severe hypotension at admission
Dane et al. [4]	US	Not reported	Not reported	No known liver disease or hypercoagulability risk factor (otherwise unknown)	Not reported	Not reported	Not reported	Not reported
La Mura et al. [5]	Italy	72, M	Inpatient (COVID-19 Unit)	Parkinson disease, anxious-depressive syndrome, and mild vascular dementia	Not reported	6 days	Enoxaparin 4000 UI qd	Fever, jaundice, and obnubilation at admission, followed by mild abdominal pain with bloating and constipation, periumbilical tenderness, and no rebound reaction nor ascites at clinical examination
Osofu et al. [6]	US	55, M	Outpatient	Hyperlipidemia	Not reported	Occasional finding, no symptom/sign of SVT at diagnosis	None	Fever, shortness of breath, and altered mental status during 3 days
Franco-Moreno et al. [7]	Spain	27, M	Outpatient	None	Negative RT-PCR on nasopharynx swab. Diagnosis of SARS-CoV-2 infection based on serological test showing IgG positivity	21 days	None	Fever and dry cough during 3 days, without nausea, vomiting or diarrhea. Tenderness in the right upper quadrant at clinical examination

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Table 1 (*continued*)

Del Hoyo et al. [8]	Spain	61, F	Outpatient	T2DM	Positive RT-PCR on nasopharynx swab and serological test	Symptoms/signs of SVT at COVID-19 onset	None	Severe acute abdominal pain and vomiting
Qing Pang et al. [9]	Singapore	30, M	Outpatient	None	Positive RT-PCR on nasopharynx swab	Symptoms/signs of SVT at COVID-19 onset	None	Colicky abdominal pain and vomiting during 2 days
Low et al. [10]	US	51, M	Not reported	Not reported	Not reported	Not reported	Heparin (not specified)	Large volume of hematemesis following initiation of heparin for a lower extremity deep vein thrombosis
Jafari et al. [11]	Iran	26, M	ICU	Asthma	Positive RT-PCR on nasopharynx swab	7 days	Not reported	Respiratory distress and fatigue during 7 days, followed by severe abdominal pain located in the right upper quadrant
Lari et al. [12]	Kuwait	38, M	Outpatient	None	Positive RT-PCR on nasopharynx swab	Symptoms/signs of SVT at COVID-19 onset	None	Progressively worsening abdominal pain, nausea, intractable vomiting, and shortness of breath during 2 days. Tachycardia, respiratory distress, and abdominal pain out of proportion to the palpation at clinical examination
Filho et al. [13]	Brazil	33, M	Outpatient	Obesity	Positive RT-PCR on nasopharynx swab	11 days	None	Dry cough, fever, and fatigue during 11 days, followed by severe low back pain radiating to the hypogastric region
Thuluva et al. [14]	Singapore	29, M	Outpatient	None	Positive RT-PCR on nasopharynx swab	Symptoms/signs of SVT at COVID-19 onset	None	Lefts-side colicky abdominal pain associated with nausea, vomiting, and decreased appetite

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Table 1 (*continued*)

Abeysekera et al. [15]	UK	42, M	Outpatient	Chronic hepatitis B (undetectable viral load on Entecavir), and prior trauma-related splenectomy	Negative RT-PCR on nasopharynx swab. Diagnosis of SARS-CoV-2 infection based on serological test	14 days	None	Fever and cough during 14 days, followed by sudden constant non-radiating right hypochondrial pain
Aleman et al. [16]	Ecuador	44, M	Outpatient	None	Positive RT-PCR on nasopharynx swab	7 days	None	Severe abdominopelvic pain of progressive and insidious onset, after initial respiratory symptoms
Rodriguez-Nakamura et al. [17]	Mexico	42, F	Outpatient	Extreme obesity, and ventriculoperitoneal shunt due to a partially resected craniopharyngioma	Negative RT-PCR on nasopharynx swab. Suspicion of COVID-19 based on clinical features and pulmonary findings at imaging	Symptoms/signs of SVT at COVID-19 onset	None	Colic abdominal pain associated with a difficulty with passing gases and a weeklong constipation
Hambali et al. [18]	Malaysia	55, M	Outpatient	Active smoking	Positive RT-PCR on nasopharynx swab	Symptoms/signs of SVT at COVID-19 onset	None	Abdominal distension and bilateral leg swelling for 10 days
Alharthy et al. [19]	Saudi Arabia	45, M	Outpatient	None	Positive RT-PCR on nasopharynx swab	Symptoms/signs of SVT at COVID-19 onset	None	Fever, cough, dyspnea, diarrhea, vomiting and abdominal pain
Goodfellow et al. [20]	UK	36, F	Outpatient	Laparoscopic Roux-en-Y Gastric Bypass, asthma and depression	Positive RT-PCR on nasopharynx swab	5 days	None	Epigastric pain radiating through to the back with nausea
Rozenshteyn et al. [21]	US	50, M	Outpatient	Alcohol-associated cirrhosis	Positive RT-PCR on nasopharynx swab	Not reported	Prophylaxis for deep venous thrombosis (not specified)	Altered mental status, followed by right upper quadrant abdominal pain

List of abbreviations ICU intensive care unit; ISH immunohistochemistry; NASH non-alcoholic steatohepatitis; RT-PCR real-time reverse transcription polymerase chain reaction; SVT splanchnic vein thrombosis; T2DM type 2 diabetes mellitus.

Table 2
Management and outcomes of the 21 patients included.

Author	Imaging test for SVT diagnosis	Sites of SVT	Other sites	Other findings at imaging	Diagnostic workup for inherited or acquired thrombophilia	Therapy	Outcome
De Barry et al. [1]	CT scan	Right portal vein thrombosis originating from the distal part of the upper mesenteric vein extended to the spleno-mesenteric trunk	Proximal thrombosis of the upper mesenteric and jejunal arteries	Features of bowel ischemia of the cecum and small intestine, small amount of liquid in the peritoneal cavity	Not reported	Bowel resection, thrombolysis and thrombectomy of the upper mesenteric artery	Death
Ignat et al. [2]	CT scan	Superior mesenteric vein and portal vein thrombosis	None	Signs of segmental portal hypertension with gastric varices and portal cavernoma	The diagnosis of essential thrombocythemia was established	Anticoagulation (not specified)	Clinical worsening due to segmental small bowel ischemia necessitating resection. Patient discharged thereafter
Norsa et al. [3]	CT scan	Superior mesenteric vein thrombosis	Inferior vena cava thrombosis	High suspicion of small bowel ischemia	Not reported	Bowel resection	Death
Dane et al. [4]	DUS	Main portal vein thrombosis extending to the right and left portal veins	Not reported	Not reported	Not reported	Not reported	Not reported
La Mura et al. [5]	CT scan	Total occlusion of the left portal venous system and the secondary branches of the right portal vein	None	Large area of transient hepatic attenuation differences in the liver segments supplied by thrombosed branches	Protein C, Antithrombin, Factors II and VII were normal. Otherwise, the authors report that inherited and acquired thrombophilia was excluded with no further specification	Enoxaparin 100 UI/kg bid	Not reported
Osofu et al. [6]	CT scan	Thrombosis of the main right anterior and posterior divisions of the right portal vein	None	Wedge-shaped peripheral defect suggestive of ischemia	Antithrombin, Lupus anticoagulant, Proteins C and S were normal	Apixaban 5 mg bid	Discharge
Franco-Moreno et al. [7]	CT scan	Thrombosis of the right branch of the portal vein	None	None	JAK2, Factor V Leiden, and prothrombin G20210A mutations, antiphospholipid antibodies, Proteins C and S, Antithrombin and Factor VIII levels, flow cytometric testing for paroxysmal nocturnal hemoglobinuria were negative	Enoxaparin 100 UI/kg bid, followed by acenocoumarin	Discharge

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Table 2 (*continued*)

Del Hoyo et al. [8]	CT scan	Right hepatic vein thrombosis and complete thrombosis of the spleno-portal axis	None	Ileo-jejunal and right colon wall edema as signs of tissue hypoperfusion changes	Lupus anticoagulant antibodies were detectable at low titer, whereas V617F JAK2, Factor V Leiden, prothrombin G20210A mutations, anticardiolipin IgG and antibeta2-glycoprotein antibodies were negative	Enoxaparin 100 UI/kg bid	Rectal bleeding and death
Qing Pang et al. [9]	CT scan	Superior mesenteric vein thrombosis	None	Diffuse mural thickening and fat stranding of multiple jejunal loops	Lupus anticoagulant was positive	Enoxaparin 100 UI/kg bid	Clinical worsening due to tight stenosis of mid jejunum caused by congenital adhesion band necessitating excision and bowel resection. Patient discharged thereafter to a community isolation facility
Low et al. [10]	CT scan	Non-occlusive thrombus in the right and left portal veins	Lower extremity deep vein thrombosis	Gastric pneumatosis, portal venous gas	Not reported	Nasogastric decompression and intravenous heparin	Unknown. According to the authors, the patient had resolution of the intramural gastric and portal venous gas, with no residual portal vein thrombosis at imaging one week later
Jafari et al. [11]	CT scan	Portal vein thrombosis	None	Intraperitoneal fluid	Not reported	Continuous intravenous heparin infusion (1000 UI/h)	Discharged
Lari et al. [12]	CT scan	Extensive thrombosis of the portal, splenic, superior and inferior mesenteric veins	Pulmonary embolism	High suspicion of ischemia of the mid-portion of the small bowel	According to the authors, the patient was tested for coagulopathies by serological testing, which were negative with low/clinically insignificant titers (with no further specification)	Heparin therapy (not specified), bowel resection, ECMO	Still in ICU at the time of manuscript submission
Filho et al. [13]	CT scan	Inferior mesenteric vein thrombosis	None	Infiltration of the adjacent adipose planes	Not reported	Enoxaparin (therapeutic dose), warfarin after 5 days	Discharged

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Table 2 (*continued*)

Thuluva et al. [14]	CT scan	Superior mesenteric vein thrombosis	None	Diffuse small bowel wall thickening involving the jejunal loops, with adjacent mesenteric fat stranding secondary to mesenteric venous congestion with no bowel wall ischemia, minor ascites	Not reported	Low molecular weight heparin 100 UI/kg bid	Unknown. According to the authors, the patient showed an improvement of abdominal pain, and resumed a normal diet by day 6 of hospitalization
Abeysekera et al. [15]	Suspected at DUS, confirmed at CT scan	Portal vein and proximal superior mesenteric vein thrombosis	None	Expansion and surrounding inflammatory stranding	According to the authors, the patient was tested for thrombophilia, which excluded inherited and acquired conditions like antiphospholipid syndrome, myeloproliferative disorders and paroxysmal nocturnal hematuria.	Apixaban 5 mg bid	Unknown. According to the authors, an imaging 6 weeks later showed an established portal vein thrombosis with collateralization extending into the upper abdomen, the patient being asymptomatic
Aleman et al. [16]	DUS and CT scan	Superior mesenteric, splenic, and portal vein thrombosis	None	Small bowel loop dilatation and mesenteric fat edema	Not reported	Enoxaparin, followed by warfarin	Discharge
Rodriguez-Nakamura et al. [17]	CT scan	Portal vein and mesenteric veins thrombosis	None	Ileum, wall edema and perfusion alterations due to stress, absence of a defined transition zone, peritoneal fat stripes, and abdominopelvic collection in the mesentery	Not reported	Bowel resection	Death
Hambali et al. [18]	CT scan	Portal vein thrombosis	None	Multifocal liver lesions	Not reported	No anticoagulation therapy reported	Discharge

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Table 2 (*continued*)

Alharthy et al. [19]	CT scan	Portal vein thrombosis	Pulmonary embolism	Thickened bowel wall	According to the authors, the patient was tested negative for lupus anticoagulant, antiphospholipid antibodies, anti-neutrophil cytoplasmic antibodies and thrombophilia screening (i.e. levels of proteins C and S, homocysteine, factor V Leiden)	Bowel resection, followed by continuous renal replacement therapy, full anticoagulation therapy (not specified)	Discharge
Goodfellow et al. [20]	CT scan	Superior mesenteric vein thrombosis	None	Diffuse infiltration of the mesentery suggestive of mesenteric edema and wall thickening in the small bowel	According to the authors, the patient was tested negative for JAK-2, Calreticulin, and MPL, lupus, anti-phospholipid syndrome, and paroxysmal nocturnal hemoglobinuria	Continuous intravenous heparin infusion, followed by dalteparin	Discharge
Rozenshteyn et al. [21]	Suspected at DUS, confirmed at CT scan	Extensive veno-occlusive disease involving the inferior vena cava and hepatic veins, consistent with Budd-Chiari syndrome	None	None	Not reported	Variceal band ligation prior to initiation of anticoagulation therapy (not specified)	Not reported

List of abbreviations CT computed tomography; DUS Doppler ultrasound; ECMO extracorporeal membrane oxygenation; SVT splanchnic vein thrombosis

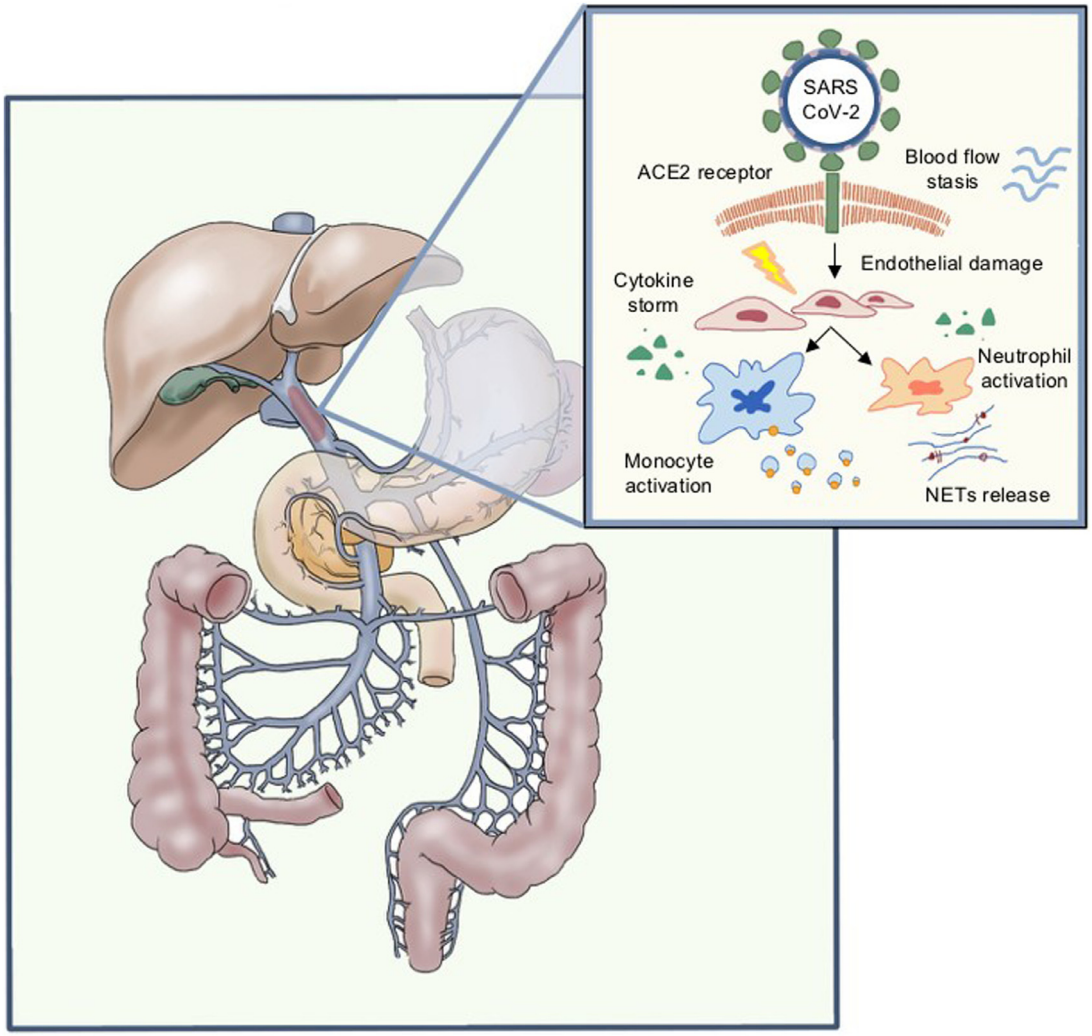

Fig. 1. Hypothesis of pathological mechanisms of SARS-CoV-2 infection and splanchnic vein thrombosis. *List of abbreviations* ACE2 Angiotensin-converting enzyme II; NETs neutrophil extracellular traps; SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2

age of patients developing venous thromboembolic events other than SVT during COVID-19 ranges between 60 and 70 years [35,36]. Concerning SVT in other clinical scenarios, the mean age of patients is estimated between 50 and 60 years in case of PVT [37], and between 70 and 79 years for MVT [38]. Therefore, the data reported herein seem to suggest an uncommonly young age in patients developing SVT and concomitant COVID-19.

Clinical presentation of SVT was often unspecific, especially in a context of multiorgan involvement and failure, making its prompt identification challenging. Typical presentation for patients without COVID-19 includes abdominal pain, reported in almost half of cases, gastrointestinal bleeding and ascites [39]. Abdominal pain was also the main reported symptom in the reported series, followed by vomiting and fever.

As for the known risk factors for SVT, only two patients had known liver cirrhosis. In one case, imaging tests performed at admission documented multifocal liver lesions consistent with hepatocellular carcinoma in the setting of newly discovered chronic hepatitis B. Advanced liver disease is itself a risk factor for SVT. Defining a clear etiological role of SARS-CoV-2 different in this population from SVT in non-cirrhotic patients remains unclear. However, it is likely that SARS-CoV-2 represents a further trigger in this context as well. Indeed, a worsening effect of COVID-19 on the prognosis of patients with cirrhosis is well established and progression of PVT in patients despite prophylactic therapy with LMWH has been reported [40].

Interestingly, in one case COVID-19 diagnosis was possible with RNAs in situ hybridization technique applied to the resected small bowel, suggesting that local inflammation due to SARS-CoV-2 infection might be a major trigger in the development of SVT for these patients.

The diagnostic workup for inherited or acquired thrombophilia led in one case to a new diagnosis of ET, while positive LACs were found in two patients. In non-cirrhotic SVT, the mean prevalence of JAK2 V617F mutation ranges between 41.1 and 27.7%, while the mean prevalence of MPN is estimated at 40.9% and 31.5% for BCS and PVT, respectively. Additionally, for almost 20% of the subjects with SVT, JAK2 V617F screening identified MPN in patients otherwise with no typical feature of MPN [41].

With regard to LAC positivity, recent observations have suggested that single LAC positivity is a common finding during the acute phase of SARS-CoV-2 infection, without a clear causal relationship with thrombotic events. Conversely, other high-risk thrombophilia conditions, such as triple antiphospholipid antibodies positivity or high anticardiolipin/antibeta2-glycoprotein I antibodies, have rarely been described in this setting [42]. Importantly, since these findings have often been transient, unconfirmed at later measurements and not consistently associated with throm-

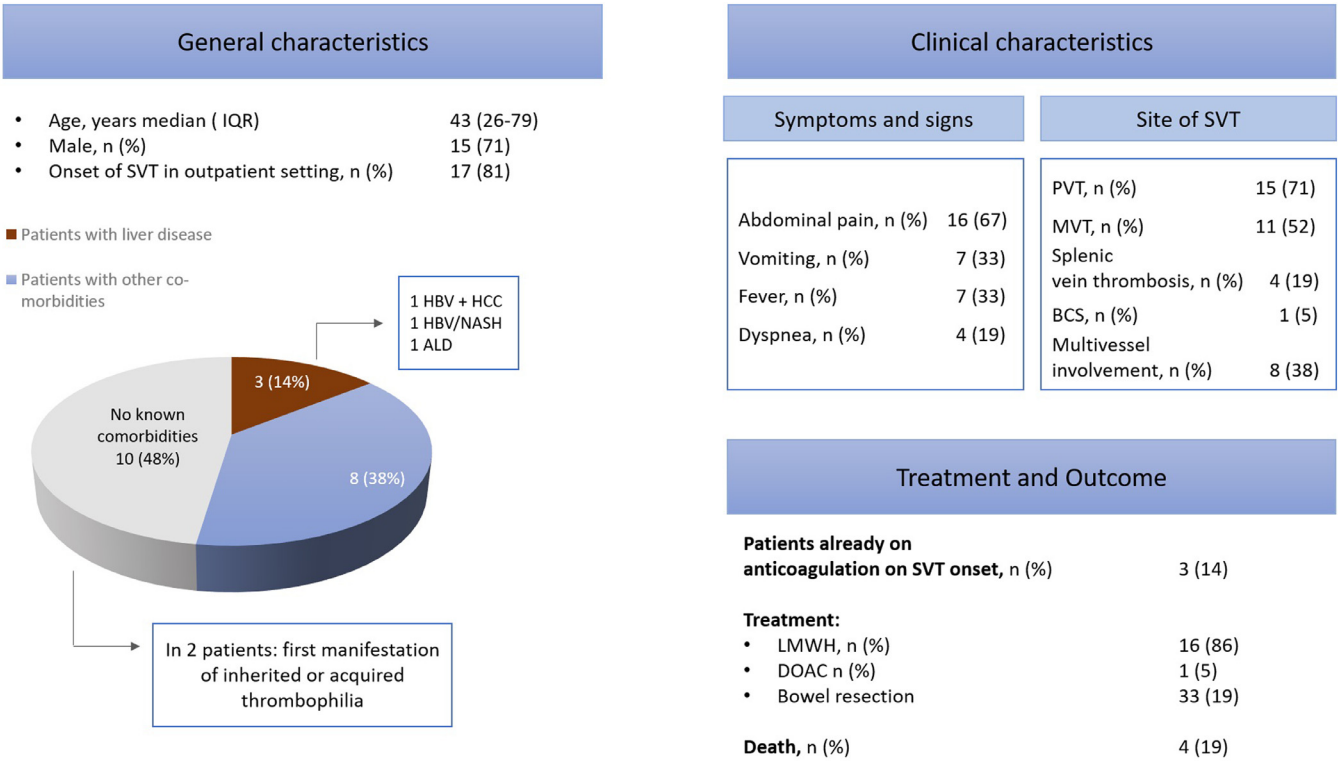

Fig. 2. General and clinical features, management and outcomes in the SVT patients presented in this systematic review. *List of abbreviations* BCS Budd-Chiari syndrome; LMWH low molecular weight heparin; MVT mesenteric vein thrombosis; PVT portal vein thrombosis; SVT splanchnic vein thrombosis; HCC hepatocellular carcinoma, HBV hepatits B virus; ALD alcohol liver disease

botic events, they may not be an adequate screening tool for acquired thrombophilia in the acute phase of the disease [43].

In the here reviewed cases, SVT was assessed using DUS imaging only for one patient, whereas in the rest of the cases CT scans ruled out the diagnosis. One patient, a young woman who was later on diagnosed of ET, showed signs of cavernous transformation of the portal vein and large porto-systemic collaterals, suggesting the presence of an acute on chronic thrombosis. DUS is a validated technique in detecting SVT with an accuracy up to 90% for diagnosing PVT, cavernous transformation of the PV and BCS [44], although the sensitivity of DUS is lower for mesenteric and splenic veins [45]. CT scan or similar cross-sectional imaging should be always considered as diagnostic tool, which may also be used to investigate the presence of signs of bowel ischemia [46] and assess the extent of involvement of all the vessels of the PV system, since involvement of more than one vessel indicates a worse prognosis [47,48]. In 8 of the SVT here reviewed cases, thrombosis involved more than one vessel.

Of note, three patients were on anticoagulation at SVT diagnosis, of whom one at therapeutic dose for concomitant deep venous thrombosis (unclear if in the outpatient or inpatient setting). One patient was receiving LMWHs at standard prophylactic dose in a COVID-19 Unit, and another one in the outpatient setting. In the only reported case of SVT occurring during ICU stay, the presence of pharmacological prophylaxis of thrombosis was not reported. Previous research suggested that the incidence of thrombotic complications in ICU patients with COVID-19 infections is remarkably high despite anticoagulant therapy at standard prophylactic dose [49]. Notwithstanding this, recent evidence on patients admitted to the ICU with COVID-19 showed that intermediate-dose prophylactic anticoagulation did not result in a significant difference in the primary outcome of a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days [50]. This might also hold true as for SVT. Ongoing trials should clarify the role of different prophylaxis strategies in the outpatient setting, including LMWHs at standard prophylactic dose, DOACs at both low and high intensity, aspirin, and sulodexide [51].

The goal of treatment of acute SVT is to achieve the patency of the vein, thus preventing bowel infarction, liver injury, and late complications of portal hypertension. The timing for starting an anticoagulant therapy is crucial in order to avoid potentially life-threatening gastrointestinal bleeding. All but five patients included in the present systematic review received anticoagulant therapy. However, four patients who underwent urgent intestinal resection have died, thus supporting the importance of immediate surgical evaluation in subjects with severe abdominal clinical presentation (e.g. bowel infarction at imaging, peritonitis, septic shock) even before considering the anticoagulant treatment. Preventive evaluation of signs of portal hypertension including gastroesophageal varices should be evaluated in a case-by-case basis in this context [46].

Evidence on which anticoagulant therapy should be used in patients with SVT is limited and choice is based mostly on clinical experience. UFH, LMWH and vitamin K antagonists are commonly used. The use of direct oral anticoagulants (DOACs) still remains off-label in most countries for SVT [46]. Potential malabsorption in case of intestinal ischemia should be always considered as a potential risk of lack of efficacy for oral therapy. Current recommendations for in-hospital patients with COVID-19 requiring anticoagulation suggest LMWH as first-line treatment [52], emphasizing its higher stability compared with UFH, particularly during the cytokine storm phase, and its reduced risk of interaction with antiviral drugs compared with DOACs. Indeed, antiviral therapy for COVID-19 has been reported to dramatically increase DOACs plasma levels [53]. Accordingly, the use of LMWH may constitute the most effective and safe strategy also for patients with

SVT during COVID-19. Future research is needed to clarify these aspects.

Limitations of the present systematic review include the small number of cases reported, and reporting bias (likely reporting of the most severe cases). The conclusions of the present study rely on the quality and accuracy of the reports included in the analysis.

5. Conclusions

SVT has been reported in 21 COVID-19 cases so far, and as such it can be considered as an uncommon manifestation of SARS-CoV-2 infection. However, SVT is often fatal, thereby requiring prompt recognition and treatment. Young patients and subjects without known comorbidities may be at risk of developing this complication. A high level of warning should be raised in presence of SVT-compatible symptoms in the setting of COVID-19.

Particular attention should be given to screening of inherited or acquired thrombophilia, bearing in mind the correct timing for testing. DUS and cross-sectional imaging remains essential for diagnosis and mapping of thrombosis extent in the portal venous system. Careful monitoring of potential signs of bowel ischemia should be performed, in order to provide appropriate treatment at early stages.

Future perspectives might embrace long-term follow-up of patients with SVT and COVID-19, aiming to evaluate its natural history, including development of late portal hypertension, specific histological alterations of the liver parenchyma, and vessels recanalization rates. In this sense, an international registry could be an extremely useful tool to document and group such sporadic cases, and follow-up the clinical evolution of these patients over time. Identifying the pathophysiological mechanisms underlying the relationship between SARS-CoV-2 infection and SVT may also be of great interest.

Declaration of Competing Interest

Giacomo Buso, Chiara Becchetti, Annalisa Berzigotti have no conflict of interest to declare.

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