Review Article

Etiologies of Splenic Venous Hypertension: A Review

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Abstract

Splenic venous hypertension or left-sided portal hypertension is a rare condition caused by an obstruction of the splenic vein. Usually, it presents with upper gastrointestinal bleeding in the absence of liver disease. Etiologies can be classified based on the mechanism of development of splenic vein hypertension: compression, stenosis, inflammation, thrombosis, and surgically decreased splenic venous flow. Diagnosis is established by various imaging modalities and should be suspected in patients with gastric varices in the absence of esophageal varices, splenomegaly, or cirrhosis. The management and prognosis vary depending on the underlying etiology but generally involve reducing splenic venous pressure. The aim of this review was to summarize the etiologies of splenic venous hypertension according to the mechanism of development.

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Introduction

Splenic venous hypertension (SVH) or left-sided hypertension is a rare condition that presents with upper gastrointestinal (GI) bleeding in the absence of liver disease.[1] Due to increased pressure in the splenic vein (SV), blood drains through the short gastric veins to the stomach causing the dilation of submucosal structures, resulting in gastric varices without portal venous hypertension (PVH) or esophageal varices.[1] The diagnosis of SVH should be considered in patients with upper GI variceal bleeding, splenomegaly, and unremarkable liver enzymes and function tests.[2]

The terms left-sided portal hypertension or sinistral portal hypertension have been used to describe this condition. However, these terms can be misleading because although some tributaries to the left portal vein may experience hypertension, the pressures in the left and main portal vein are typically not elevated as the etiologies are extrahepatic.[2]

Therefore, in this review, we will use the term SVH to emphasize the absence of PVH.

The true incidence of SVH is unknown as patients are typically asymptomatic, and less than 500 cases of SVH have been reported.[2] To diagnose SVH, a high index of clinical suspicion is required due to the often silent nature of the condition before presentation. For the purposes of this review, etiologies are arranged according to the mechanism of the development of SVH.

Mechanisms

The mechanisms involved in developing SVH include compression, stenosis, inflammation, thrombosis, and surgically decreased splenic venous flow.

Compression

Compression of the SV has been reported to account for 18% of SVH cases and can be caused by external compression by neighboring structures including benign neoplasms, adenocarcinoma, non-functioning neuroendocrine tumors, anatomical variants, and strangulation (Bochdalek hernia), leaving the vascular epithelium intact.[1]

Stenosis

SV stenosis, a rare mechanism of SVH, has been reported to be idiopathic, with no proposed mechanism yet. It is defined as (1) stenosis of the SV with post-stenotic dilatation; (2) absence of common causes of SV stenosis, such as pancreatitis, pancreatic tumor, cysts, thrombosis, arterial aneurysm, retroperitoneal fibrosis, or iatrogenic injury.[3]

Inflammation

Inflammation is the most common mechanism of SVH and is attributed to the proximity of the SV and pancreatitis in which autoactivation of pancreatic enzymes leads to pancreatic necrosis and vasculitis. This vasculitis triggers inflammation that can damage surrounding blood vessels or lead to SV thrombosis (SVT).[4] When exposed to thrombin stimulation, smooth muscle cells produce IL-6. Platelet-derived growth factor, released from platelet alpha granules during thrombosis, can also markedly augment IL-6 production inducing acute phase changes and response. This leads to increased concentrations of fibrinogen, PAI-1, and the inflammatory marker C-reactive protein. Thus, the local inflammatory state and thrombotic stimulation of smooth

muscle cells in the arterial wall promote systemic procoagulation and thrombosis.[5]

Thrombosis

Thrombosis occurs when natural underlying anticoagulation mechanisms such as protein C system receptors, tissue factor pathway inhibitors, and glycosaminoglycans are disrupted, leading to an inflammatory and prothrombotic state. Endothelium activation by proinflammatory cytokines such as tumor necrosis factor-alpha causes a shift from an anticoagulant to a procoagulant state. Upon activation, endothelial cells express adhesion molecules such as E-selectins and P-selectins involved in leukocyte rolling, and ICAM-1 and VCAM-1 lead to adhesion and transendothelial leukocyte migration. Adhesion of leukocytes and platelets is a key component to initiating thrombosis and propagation. Proinflammatory cytokines can elicit tissue factor production on the endothelium and monocytes leading to further thrombosis. Activation of coagulation eventually leads to the production of thrombin, factor Xa, and factor VIIa, which have pro-inflammatory properties.[6]

Major risk factors for SVT include liver cirrhosis, solid cancer, and myeloproliferative disorders. Provoked SVT caused by risk factors mentioned above accounts for 25% of cases, while unprovoked SVT accounts for 15–27% of cases. Patients with cirrhosis have an increased risk of thrombosis due to a high factor VIII/protein C ratio, increased thrombin generation, and alterations in fibrin clot structure. Solid cancer can lead to a prothrombotic state due to factors such as immobilization, surgery, chemotherapy, and central venous catheter placement as well as underlying hemostatic alterations causing a prothrombotic state. Myeloproliferative disorders increase the incidence of arterial and venous thrombosis through a multifactorial process including alterations in platelets, erythrocytes, leukocytes, and endothelial cells.[6] The V617F substitution of the JAK2 gene is strongly associated with myeloproliferative disorder and SVT as it promotes thrombosis through P-selectin overexpression leading to platelet aggregation and fibrin deposition.[7]

Surgically decreased splenic venous flow

The mainstay treatment for pancreatic cancer is surgical intervention. Patients typically undergo a pancreatoduodenectomy (PD) and a portal-superior mesenteric vein (PV-SMV) resection for clear margins. During this procedure, the SV is ligated. However, even when preserved, there can be decreased venous flow of the SV due to PV and superior mesenteric vein ligation causing vascular congestion, increased pressure within the venous system, and gastric varices with upper GI bleeding. This complication is more common in the late stages of PD as increased survival time due to surgery provides a greater length of time for the development and bleeding of varices.[8]

Etiologies categorized by mechanism

Compression

Pancreatic neuroendocrine tumor (NET): Pancreatic neuroendocrine tumors represent 1–2% of all pancreatic tumors.[9] A retrospective study conducted by Moyana *et al*. focused on pancreatic NETs and SVH. The study included patients with histologic confirmation of pancreatic NET and imaging consistent with SVT). Among the 61 patients with

pancreatic NET, eight (13%) had SVT. Four (50%) of these SVT patients met the criteria for SVH (SVT, gastric varices, patent portal vein, normal liver function, and inflammatory tests) and presented with upper GI bleeding. In all cases, the pancreatic NETs were located in the tail with invasion of the SV.[9] This study included a compilation of data on a rare entity, although a small sample size and retrospective design. Several case reports have also been published (Tables 1A and 2A).[9–25]

Lymphoma: Case reports described compression of the SV by lymphoma, presenting with variceal bleeding, absence of cirrhosis, and imaging and pathology indicative of lymphoma. In one case, high-grade-B-cell lymphoma resolved gastric varices with chemotherapy alone, while a case of large B-cell lymphoma required splenic artery embolization and chemotherapy for resolution (Tables 1A and 2A).[12,13]

Splenic artery aneurysm (SAA): SAAs account for 0.77% of all abdominal aneurysms.[26] The splenic artery is considered aneurysmal when dilation is reduced to 50% compared to normal.[14] SVH secondary to SAA has been described in a few case reports, with patients presenting symptoms such as anemia, epigastric pain, or GI bleeding. Treatment involved surgical excision of the splenic artery and splenectomy. On follow-up, one case had a resolution of gastric varices (Tables 1A and 2A).[15,16]

Bochdalek hernia: Bochdalek hernias are congenital diaphragmatic hernias resulting from a failed closure of the posterolateral diaphragm.[17,18] They present in adults with an incidence of 0.17%.[17] One reported case involved a Bochdalek hernia causing SVH by strangulation of the spleen within the hernia and subsequent venous obstruction, undergoing laparotomy and splenectomy for repair (Tables 1A and 2A).[18]

Pancreatic cysts and pseudocysts: Pancreatic pseudocysts have an incidence of 14.6–41.8% and are typically a complication of pancreatitis.[19] Due to the proximity of the pancreas and the SV, pancreatic cysts and pseudocysts can compress the SV and cause subsequent SVH.[20] There have been two reported cases that presented with abdominal pain and anemia during workup. Abdominal ultrasound (US) was used to identify pancreatic pseudocysts, confirmed with CT of the abdomen and pelvis. One patient underwent laparotomy, and the other underwent pancreatectomy and splenectomy. However, both cases lacked radiographic follow-up (Tables 1A and 2A, Fig. 1A).[20,21]

Retroperitoneal fibrosis (RF): RF is a rare condition with an annual incidence of 1.3/100,000.[22] Typically, it affects retroperitoneal structures. However, one case of RF was reported with compression of the SV leading to SVH. The patient had a previous diagnosis of retroperitoneal fibrosis and presented with new anemia. The patient underwent esophagogastroduodenoscopy (EGD) and CT of the abdomen and pelvis, which showed diffuse gastric varices and progression of the retroperitoneal mass with obstruction of the SV and splenomegaly. This was managed by splenectomy and ligation of varices, and the patient remained asymptomatic 18 months later (Tables 1A and 2A).[23]

Peripancreatic lymph node tuberculosis: There has been one reported case of peripancreatic lymph node tuberculosis causing SVH. CT of the abdomen and pelvis showed a mass in the body of the pancreas with an enlarged SV and tortuous gastric veins. EGD revealed fundal gastric varices. The patient underwent perigastric vein dissection and splenectomy. Additionally, enlarged lymph nodes were noted, with pathology consistent with necrotizing granulomatous lymphadenitis. Ziehl-Neelsen staining was positive, consistent with tuberculosis. The etiology of her SVH was secondary

Table 1. Studies on Etiologies of Splenic Vein Hypertension

A. Compression

Etiology	Prevalence	Gender Difference	Mean Age	Presentation	Means of Diagnosis	Therapy	Outcome	Follow-up	References
Pancreatic NET	1–2% of all pancreatic tumors	N/I	N/I	Abdominal pain, symptoms based on hormone produced	CT, MRI, EUS	Systemic chemotherapy, surgical resection	N/I	N/I	9
Lymphoma	N/I	N/I	N/I	Lymphadenopathy, B symptoms, symptoms based on the type of lymphoma	Tissue biopsy	Chemotherapy	N/I	N/I	25
SAA	0.77% of all abdominal aneurysms	N/I	N/I	Epigastric or left upper quadrant pain that radiates to the left shoulder	CT, MRI, contrast angiography, endoscopic US	Surgical excision of aneurysm and/or splenectomy	N/I	N/I	14
Bochdalek hernia	0.17%	N/I	N/I	Abdominal pain	US, chest x-ray, and CT abdomen	Surgical repair of the defect	N/I	N/I	17,18
Pancreatic cysts and pseudocysts	14.6–48.1%	N/I	N/I	Abdominal pain, back pain, weight loss, jaundice, and/or palpable mass	CT, MRI, endoscopic US	Distal pancreatectomy and splenectomy	N/I	N/I	20,19
RF	0.000013%	3:1 male:female ratio	64	Abdominal pain, flank pain, discomfort	CT Abdomen	Splenectomy	N/I	N/I	22
Peripancreatic lymph node tuberculosis	N/I	N/I	N/I	Abdominal pain and biliary obstruction	CT abdomen, Ziehl-Neelsen staining	N/I	N/I	N/I	24

B. Stenosis

Etiology	Prevalence	Gender Difference	Mean Age	Presentation	Means of Diagnosis	Therapy	Outcome	Follow-up	References
Idiopathic splenic vein stenosis	N/I	N/I	N/I	N/I	CT abdomen	Splenectomy	N/I	N/I	3

C. Inflammation

Etiology	Prevalence	Gender Difference	Mean Age	Presentation	Means of Diagnosis	Therapy	Outcome	Follow-up	References
Pancreatitis	15%	Male predominant	N/I	Abdominal pain, gastrointestinal bleeding	CT abdomen	Splenectomy	N/I	N/I	34,32

(continued)

Table **1**. *(continued)*

D. Thrombosis

Etiology	Prevalence	Gender Difference	Mean Age	Presentation	Means of Diagnosis	Therapy	Outcome	Follow-up	References
Pancreatic cancer	N/I	N/I	71	Painless jaundice, abdominal pain, weight loss	CT, MRI, ERCP	Surgical resection	N/I	N/I	35
Wandering spleen	N/I	N/I	N/I	Asymptomatic mass	US, CT, MRI	N/I	N/I	N/I	39
ET	4–13%	N/I	N/I	Incidental findings, fatigue, abdominal pain, insomnia, headache	Bone marrow biopsy, CBC	Splenic embolization	N/I	N/I	56
PMF	0.6–1%	N/I	69–79	Anemia, fatigue, shortness of breath	Bone marrow biopsy	N/I	N/I	N/I	42
FVL	3–8%	N/I	N/I	Incidental finding, arteriovenous thromboembolism	Genetic testing	Anticoagulation	N/I	N/I	48
SCT	8% in African Americans and 0.2% in Caucasians	N/I	N/I	Asymptomatic, occlusive pain	Hemoglobin electrophoresis	Conservative therapy, symptomatic management	N/I	N/I	51
PNH	N/I	N/I	N/I	Fatigue, dyspnea, dark urine	Flow cytometry	Supportive measures, Eculizumab	N/I	N/I	53

E. Surgically Decreased Splenic Venous Flow

Etiology	Prevalence	Gender Difference	Mean Age	Presentation	Means of Diagnosis	Therapy	Outcome	Follow-up	References
Pancreatoduodenectomy	N/I	None	58	GI bleeding	CT abdomen, EGD	Splenectomy, colectomy	N/I	N/I	8,60, 61

CBC, complete blood count; CT, computed tomography; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; ET, essential thrombocythemia; EUS, endoscopic ultrasound; FVL, factor V Leiden; MRI, magnetic resonance imaging; N/I, no information; NET, neuroendocrine tumor; PMF, primary myelofibrosis; PNH, paroxysmal nocturnal hemoglobinuria; RF, retroperitoneal fibrosis; SAA, splenic artery aneurysm; SCT, sickle cell trait; US, ultrasound.

Table 2. Summary of Case Reports

A. Compression

Etiology	Number of cases	Mean Age	Presentation	Means of Diagnosis	Therapy	Outcome	Follow-up	References
NET	3	74.5	Epigastric pain, upper GI bleeding (hematemesis, melena)	CT abdomen	Systemic chemotherapy, complete resection of pancreatic NET	Resolution of gastric varices on EGD and CT, 3.6% mortality	3 months, 6 months, 8.5 years	9,10,11
Lymphoma	2	75	Upper GI bleed (hematemesis, melena)	CT Abdomen, US-guided biopsy, MRI, CT-guided biopsy, PET scan	Systemic chemotherapy, splenic artery embolization	No recurrence of GI bleeding, returned splenic vein patency	6 months	12,13
SAA	2	31.5	Epigastric pain, upper GI bleed (hematemesis), fatigue, anemia	CT abdomen/pelvis	Surgical excision of splenic artery and splenectomy	Resolution of varices on EGD and resolution of anemia	8 months	15,16
Bochdalek hernia	1	21	Chronic cramping abdominal pain, fatigue	CT abdomen/pelvis	Laparotomy for defect repair and splenectomy	Asymptomatic	2 months, no radiographic follow-up	18
Pancreatic cysts and pseudocysts	2	58.5	Abdominal pain, melena, abdominal distension	US abdomen, CT abdomen, intraoperative exam and biopsy	Distal pancreatectomy and splenectomy	Asymptomatic	2 months, no radiographic follow-up	20,21
RF	1	77	Anemia	CT abdomen, biopsy of the retroperitoneal mass	Splenectomy, ligation of varices	Asymptomatic	18 months, no radiologic follow-up	23
Peripancreatic lymph node tuberculosis	1	29	Chronic melena	Positive interferon-gamma release assay, CT abdomen/pelvis/chest, Ziehl-Neelsen staining	Perigastric vein dissection and splenectomy	N/I	N/I	24

B. Stenosis

Etiology	Number of cases	Mean Age	Presentation	Means of Diagnosis	Therapy	Outcome	Follow-up	References
Idiopathic splenic vein stenosis	3	42.6	Upper GI bleeding (melena, hematemesis), epigastric pain	CT abdomen, transhepatic splenic and portal venography	Splenectomy, propranolol	Resolution of gastric varices on EGD after splenectomy, recurrent melena after 6 weeks of propranolol	3 months	3,27,28

C. Inflammation

| Etiology	Number of cases	Mean Age	Presentation	Means of Diagnosis	Therapy	Outcome	Follow-up	References
Pancreatitis	3	54	Abdominal pain, GI bleeding (melena, hematemesis)	CT abdomen, MRI abdomen	Splenectomy, splenic artery embolization	Resolution of GI bleeding	29 months	30,32,33

(continued)

Table 2. *(continued)*

				D. Thrombosis				
Etiology	**Number of cases**	**Mean Age**	**Presentation**	**Means of Diagnosis**	**Therapy**	**Outcome**	**Follow-up**	**References**
Pancreatic cancer	3	50	Abdominal pain (left upper quadrant, epigastrium)	CT abdomen/pelvis	Distal pancreatectomy and splenectomy	2 lost to follow up, 1 comfort measure/death	N/I	36–38
Wandering spleen	3	74	Lower abdominal pain, GI bleeding	Abdominal US, CT abdomen/pelvis	Splenic vein thrombectomy and splenectomy	Resolution of GI bleeding	Regular follow-up	39–41
ET	2	55.6	Upper GI bleeding (melena), abdominal pain	Splenic venogram, CT abdomen	Splenic artery embolization, laparoscopic gastric devascularization, partial splenic embolization	Resolution of bleeding and gastric varices	6 months	43,44
PMF	3	57.6	Upper GI bleeding (hematemesis, melena), fatigue	CT abdomen, bone marrow biopsy	Splenectomy, gastric devascularization, splenic artery embolization	Resolution of varices and bleeding on EGD	3 months and 1 year	45–47
FVL	2	50	Abdominal pain, weight loss	CT abdomen, hypercoagulable workup	IV heparin	Recanalization of the splanchnic venous system on CT and US	1, 5, 14 and 36 months	49,50
SCT	3	25.5	Abdominal pain, vomiting	CT abdomen, hemoglobin electrophoresis	Conservative management (rest, analgesia), splenectomy, gene therapy	Symptom resolution	N/I	51,52, 57
PNH	3	38	Abdominal pain, dark urine	CT abdomen, CTA abdomen, flow cytometry	IV heparin followed by oral anticoagulation, eculizumab	Reduction of intravascular hemolysis	3 months	54,55, 58
				E. Surgically Decreased Splenic Venous Flow				
Etiology	**Number of cases**	**Mean Age**	**Presentation**	**Means of Diagnosis**	**Therapy**	**Outcome**	**Follow up**	**References**
Pancreatoduodenectomy	3	58	Upper GI bleeding (melena), hypovolemic shock	CT abdomen/pelvis, trans-splenic venography	Splenic artery embolization	Resolution of bleeding on CT	6 months	8,60,61

CT, computed tomography; CTA, computed tomography angiography; EGD, esophagogastroduodenoscopy; ET, essential thrombocythemia; FVL, factor V Leiden; GI, gastrointestinal; IV, intravenous; MRI, magnetic resonance imaging; N/I, no information; NET, neuroendocrine tumor; PMF, primary myelofibrosis; PNH, paroxysmal nocturnal hemoglobinuria; RF, retroperitoneal fibrosis; SAA, splenic artery aneurysm; SCT, sickle cell trait; US, ultrasound.
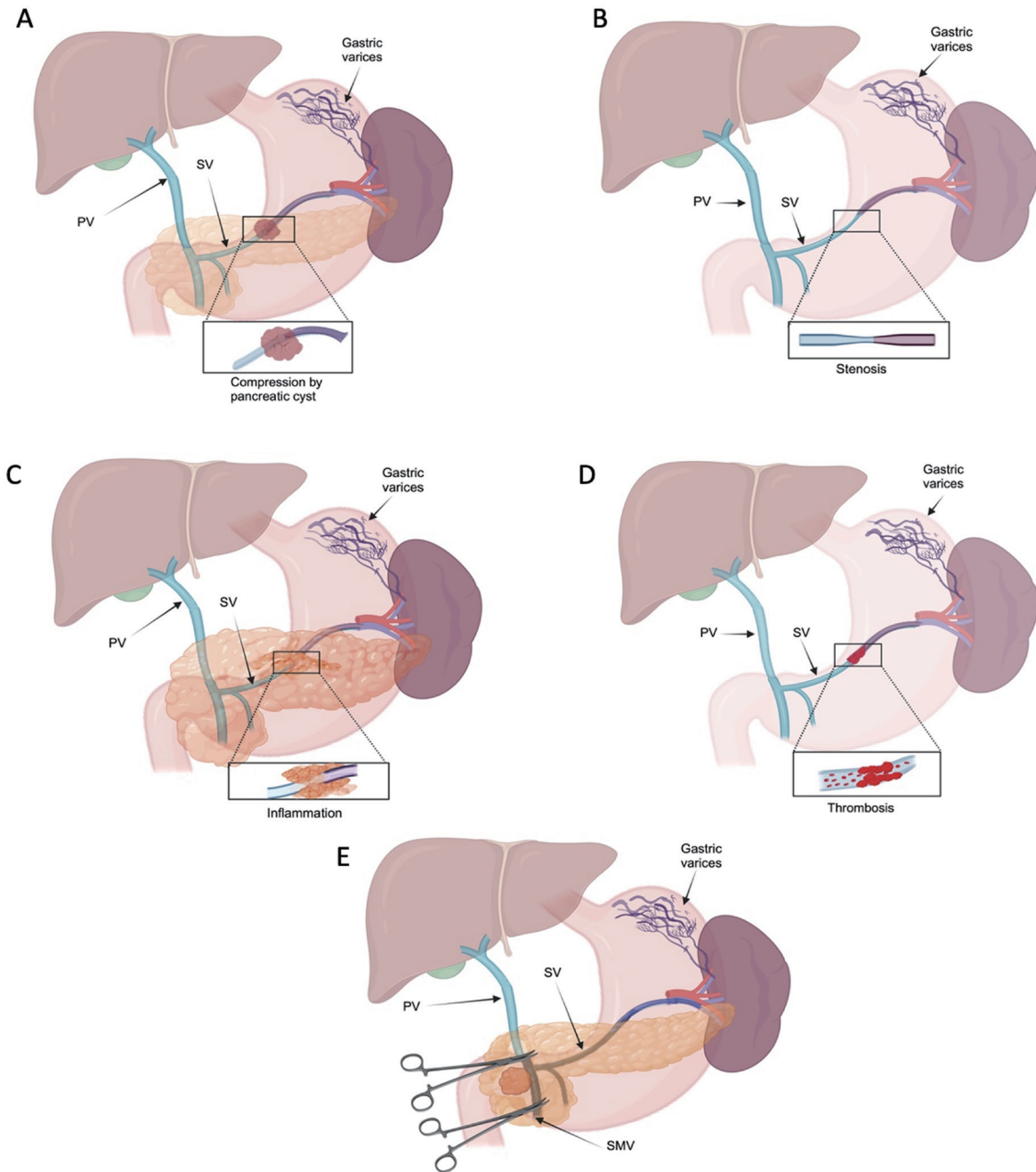
Fig. 1. Mechanisms of development of splenic vein hypertension. (A) Compression. Pancreatic cysts compress the splenic vein, increasing venous flow in the gastric veins and forming varices. Other causes of compression include pancreatic NET, lymphoma, SAA, Bochdalek hernia, enlarged lymph nodes, and RF. (B) Stenosis. Idiopathic splenic vein stenosis increases the venous blood flow in the gastric veins, forming varices. (C) Inflammation. Pancreatitis can lead to fibrosis with subsequent occlusion of the splenic vein, leading to increased flow to the gastric veins and the formation of varices. (D) Thrombosis. ET and PMF can lead to splenic vein thrombosis, increasing blood flow in the gastric veins with varix formation. (E) Surgically decreased splenic venous flow. PV-SMV resection performed in the setting of a pancreatic tumor can lead to increased congestion of the splenic vein with subsequent formation of gastric varices. ET, essential thrombocythemia; NET, neuroendocrine tumor; PMF, primary myelofibrosis; PV-SMV, portal vein-superior mesenteric vein; PV, portal vein; SAA, splenic artery aneurysm; SMV, superior mesenteric vein; SV, splenic vein; SVH, splenic venous hypertension.

to either enlarged lymph node compression or scarring from caseous necrosis (Tables 1A and 2A).[24]

Stenosis

Idiopathic SV stenosis: Few cases of SV stenosis have been reported; therefore, the exact incidence is unknown. The re-

ported cases have shown variable presentations, including epigastric pain, melanotic stools, or hypotensive shock due to melena or hematemesis. In all cases, EGD revealed gastric varices, and CT of the abdomen and pelvis showed SV stenosis. One of three cases was managed with splenectomy with surveillance EGD, and two cases were managed con-

servatively with propranolol. One of the patients managed conservatively eventually required splenectomy due to continued melena (Tables 1B and 2B, Fig. 1B).[3,27,28]

Inflammation

Madsen *et al*. characterized 209 patients with SV obstruction, defined as the partial or total occlusion of the SV with normal superior mesenteric and portal veins. SV occlusion was found to be more frequent in males (89%) with a median age of 48.[29]

Likewise, a retrospective study of 633 patients with acute pancreatitis (AP) was performed. Data revealed that 3.3% had SVH (established by imaging), with 17 males and four females having a mean age of 45. SVH was more frequent in severe AP versus mild cases (47.8% vs. 0.6%, *p*=0.000), respectively. The statistical power of this study was a strength, although the lack of endoscopic evaluation was a limitation.[30] A larger study of 825 patients with moderate-to-severe pancreatitis identified risk factors for SVH, including recurrent pancreatitis, male gender, smoking, glucose >10 mmol/L, and hypertriglyceridemia.[31] A strength of this study was the large sample size, but a weakness was the retrospective design, with the possibility of patients being lost to follow-up.

A retrospective case-control study analyzed dynamic changes in gastric varices, independent risk factors for SVH, and the relationship between the patency of portosplenomesenteric veins and SVH. Patients were included if they had moderate-to-severe acute AP or severe AP according to the 2012 Atlanta Classification. Patients were excluded if they had pancreatic cancer, chronic pancreatitis, cirrhosis, chronic liver disease, or a history of gastric, splenic, or pancreatic surgery. A total of 316 patients were eligible, with 94 meeting the criteria for SVH (absence of liver disease and presence of gastric varices) and 94 matched controls. Patients underwent CT of the abdomen and pelvis within two weeks of the onset of AP to identify collateral vessels, gastric varices, and patency of the portal venous system. They were followed for at least one year after discharge with interval CT imaging. The most commonly found gastric varices were fundal (90.4%), left gastroepiploic (70.2%), middle colonic (68.1%), gastric coronary (61.7%), and short gastric (57.4%). Over a year, the diameter of the varices increased. SVH was detected on average nine weeks after AP, with 38.3% detected within one month, 55.3% between one month and a year, and 6.4% after more than a year. Risk factors for SVH included male sex, body mass index >27.5 kg/m2, stenosis of SV, and occlusion of the SV.[32] The results were statistically significant and adjustments were made for possible confounding variables.

In contrast, Xie *et al*. performed a retrospective study to identify the prevalence and characteristics of SVH using MRI in patients with AP. A total of 633 patients underwent abdominal MRI, with SVH diagnosed based on the absence of liver disease and the presence of gastric varices and/or splenomegaly. The average age of the patients was 50; 336 were male and 297 were female. Among them, 80.6% had edematous pancreatitis, and 19.4% had necrotizing pancreatitis. SVH was detected in 3.3% of cases, with an average age of 44, more common in males (17 cases) than females (four cases). The etiology of SVH was SVT in 14 cases and SV stenosis in seven cases. Gastric varices were present in all patients, with short gastric varices in 61.9%, coronary varices in 42.9%, and fundal varices in 19%. The prevalence of SVH was 0.6% in mild pancreatitis, 2.29% in moderate pancreatitis, and 47.8% in severe pancreatitis.[30] The study's strength lay in its large sample size, while limi-

tations included a lack of endoscopic data and consecutive follow-up.

Chronic pancreatitis can also lead to SVH. Ru *et al*. performed a retrospective study involving 89 patients with SVH due to chronic pancreatitis, compared with 178 control patients with chronic pancreatitis and normal portal pressures. SVH was diagnosed based on collateral vessels seen on CT or gastric fundal varices observed on EGD, with or without splenomegaly, and after excluding other portal hypertension causes. SVH was identified in 2.7% (89/3,358) of patients, with an average age of 44 and a predominance of male patients. Risk factors included a history of AP (*p*=0.010), pseudocysts (*p*<0.001), alcohol consumption (*p*=0.030), and diabetes mellitus (*p*<0.001). Variceal bleeding was present in 19.1% (17/89) of SVH patients, with hematemesis in 58.8% (10/17) while melena in 76.5% (13/17).[33] The study's retrospective study design precluded calculating the incidence of SVH (Tables 1C and 2C, Fig. 1C).[30,32,33,34]

Thrombosis

Pancreatic cancer: Solid pseudopapillary tumors of the pancreas are rare, accounting for approximately 3% of pancreatic tumors.[35] These tumors have been associated with SVH due to SVT. Of the few reported cases, all presented with abdominal pain. In one case, the abdominal US showed a large hypoechoic mass in the pancreatic tail with SVT. CT of the abdomen and pelvis in all cases revealed a mass in the pancreatic body and/or tail with SVT and, in some, splenomegaly. Two of the three cases were managed with distal pancreatectomy and splenectomy, while one was complicated by hematemesis and melena. Both cases managed with distal pancreatectomy and splenectomy lacked radiological or endoscopic follow-up (Tables 1D and 2D, Fig. 1D).[35–58]

Wandering spleen: Wandering spleen, or ectopic spleen, is a clinical entity secondary to a lack of or underdeveloped splenic ligaments, which leads to splenic migration in the abdominal cavity. It predisposes to splenic torsion and SVT, leading to SVH.[39] A review of 20 case reports found that GI bleeding was the most common chief complaint (45%), followed by abdominal pain (40%). Gastric varices were observed in 90% of the patients, 30% had splenic varices, and no esophageal varices were present. The diagnosis of varices was primarily made by EGD (60%), although 25% were diagnosed by imaging. SVT occurred in 15% of the patients, whereas 20% had splenic infarction.[40] The study had a small sample size. Several case reports have also been published (Tables 1D and 2D).[39,41]

Essential thrombocythemia: Essential thrombocythemia is a myeloproliferative neoplasm characterized by *JAK/STAT* pathway activation, leading to elevated platelet levels with an increased risk of thrombosis, including in the SV with consequent SVH. The estimated prevalence of SVT is 4% to 13%.[42] Three cases presented with various symptoms, including melena, abdominal pain, or incidental findings. EGD in all cases revealed isolated gastric varices with or without a red color sign. CT of the abdomen revealed SVT, splenomegaly, and dilated intra- and perigastric veins in two cases. In another case, a CT angiogram was used and showed varicosity of the SV without detected thrombosis, but a splenic venogram later confirmed the presence of SVT. Two of the three cases were managed with splenic artery embolization, and another was managed with laparoscopic gastric devascularization. In all cases, patients remained asymptomatic upon follow-up at three or six months (Tables 1D and 2D).[43,44]

Primary myelofibrosis (PMF): PMF is a myeloproliferative neoplasm characterized by *JAK/STAT* pathway activa-

tion, leading to a proliferation of myeloid cells and a procoagulatory state predisposing to SVT and subsequent SVH. The estimated prevalence of SVT is reported at 0.6–1.0%.[42] Patients presented with symptoms of hematemesis, melena, or fatigue. EGD in two cases was remarkable for bleeding gastric varices, one of which was specifically nonresponsive to injection sclerotherapy with ethanolamine. CT of the abdomen and pelvis and/or venography showed SV stenosis or thrombosis, splenomegaly, and gastric varices. One case was managed with splenectomy, one with splenectomy with gastric devascularization, and the last with percutaneous transhepatic variceal embolization. Two cases exhibited no further bleeding at three months or one year of follow-up. The last case developed recurrent hematemesis, and repeat EGD showed bleeding gastric varices, for which embolization of the splenic artery was performed, and no further bleeding was noted one year later (Tables 1D and 2D).[45–47]

Factor V Leiden (FVL): FVL is a genetic disorder characterized by a decreased response to activated protein C, which normally cleaves factor Va, leading to decreased thrombin generation. This mutation results from a guanine-to-adenine substitution at nucleotide 1691 in the factor V gene, causing resistance to activated protein C and increased thrombin formation. FVL has a prevalence of 3–8% and is the most common genetic risk factor for venous thromboembolism. SVT has been associated with FVL.[48] Two cases presented with abdominal pain, and one had significant weight loss. Both cases showed diffuse abdominal pain without hepatomegaly upon physical examination. Abdominal CT revealed thrombosis in the extrahepatic portal vein, mesenteric vein, and SV. In one case, EGD/colonoscopy was unremarkable. Hypercoagulable workup in both cases was remarkable for heterozygosity for FVL. Full-dose intravenous (IV) heparin was initiated in both patients with subsequent, leading to the resolution of abdominal pain. Follow-up examinations showed continued patency of the splanchnic venous system, and both patients were placed on lifelong anticoagulation (Tables 1D and 2D).[49,50]

Sickle cell trait (SCT): Sickle cell anemia is a heterozygous autosomal codominant genetic disorder manifesting as chronic hemolytic anemia. It is characterized by a homozygous genetic defect in the B chain of hemoglobin, causing an abnormal hemoglobin S (HbS). SCT is characterized by a normal hemoglobin gene from one parent and a hemoglobin S gene from another parent (HbSA). The prevalence of SCT in African Americans is reported to be 8%.[51] These patients are typically asymptomatic; however, there were two cases of SVT due to occlusion by sickle-shaped erythrocytes. Both cases presented with vomiting and abdominal pain. Abdominal US revealed SVT and splenic infarction. CT abdomen confirmed SVT with splenic infarction and otherwise normal splanchnic vasculature. Hemoglobin electrophoresis confirmed the diagnosis of SCT in both cases, and symptoms resolved with conservative therapy, including rest, hydration, and analgesia. No radiologic follow-up was reported (Tables 1D and 2D).[51,52]

Paroxysmal nocturnal hemoglobinuria (PNH): PNH is a rare genetic disorder caused by a mutation in the *PIGA* gene.[53] This gene participates in the formation of glycosylphosphatidylinositol, linking cell surface proteins to the plasma membrane of hematopoietic cells. The absence of CD55 or CD59 on the surface of red blood cells leads to complement-mediated intravascular hemolysis and consequently, thrombosis. The prevalence of PNH is 12–13 per million.[59] Two cases presented with abdominal pain and/or dark urine. In one case, abdominal CT revealed an enlarged hypodense spleen with contrast only in the subcapsular rim, while CT

angiography in another case revealed SVT. One case underwent laparotomy, revealing an enlarged, hard spleen that was removed followed by treatment with IV heparin eventually transitioned to oral anticoagulation. The other case was managed conservatively with IV heparin followed by warfarin. Three months later, this patient was started on eculizumab, which immediately reduced intravascular hemolysis. Both cases lacked radiologic follow-up (Tables 1D and 2D).[54,55]

Surgically decreased splenic venous flow

A retrospective study compiled data on the incidence of SVH and variceal bleeding in patients with PD and PV-SMV resection. Data were collected in a survey of 889 patients who underwent PD and PV-SMV resection, of whom 536 patients ranged from 27 to 89 years old with a male-to-female ratio of 289:247. They were classified into different groups based on the status of the SV, splenic artery (SA), superior mesenteric vein, and left renal vein (LRV). SVp (n=285) included patients with preservation of both the SV and SA. SVr (n=227) included those with division of the SV and preservation of the SA. SVr+SAr (n=12) included those with divisions of both the SV and the SA. SV-SMV (n=8) included the division of the SV with reconstruction to the superior mesenteric vein. LRVrec (n=4) included the division of the SV with reconstruction to the LRV. Patients underwent abdominal CT 6 and 12 months postoperatively for the surveillance of varices classified into esophageal, gastric, pancreatic, or colonic. Data showed that varices developed in 8.1% of patients in the SVp group, 33.3% in the SVr+SAr group, 37% in the SVr group, and 41.6% in the SV-SMV/LRVrec group. The overall incidence of SVH was 40%. The most frequent location of varices was gastric. Variceal bleeding occurred in the SVr group (4%) and the SV-SMV/LRVrec group (8.3%) with an overall incidence of 4%.[60] The study strengths included a large sample size with statistically significant results.

A systematic review analyzed the incidence, treatment, and preventative strategies for SVH in patients who underwent PD and PV-SMV resection. They conducted a literature search of multiple databases and included studies that reported characteristics, management, and outcomes of patients with PD and venous resection. Of 829 patients included, 7.7% had preservation of the SV, and 29.4% of those with ligation of the SV developed SVH. GI bleeding was observed in 14 patients an average of 28 months after PD with a mortality of 7.1% at one month. Eight patients were two males and six females. Varices were found in the esophagus (4), stomach (5), jejunum (2), pancreas (4), and colon (7). Three patients (21%) underwent splenectomy and one (7%) colectomy with the rest of the cases (71%) treated by endoscopic or radiologic procedures.[61] Strengths of this study included a large sample size. Limitations included a heterogeneous definition of SVH and a lack of prolonged follow-up and outcomes. Case reports have also been published (Tables 1E and 2E, Fig. 1E).[8,60,61]

Clinical presentation

SVH should be suspected in patients with upper GI bleeding, splenomegaly, and unremarkable liver function and aminotransferase tests.[1] SVH is typically found incidentally as most patients are asymptomatic (~63%) prior to bleeding.[1,62] The primary manifestation in symptomatic patients is upper GI bleeding from ruptured gastric varices (~37–54%).[1,62,63] Depending on the underlying etiology, patients may experience abdominal pain (~77%), with approximately 70% showing splenomegaly.[1,63] Patients can have hypersplenism with thrombocytopenia and pancytopenia (~23–93%).[62,63]
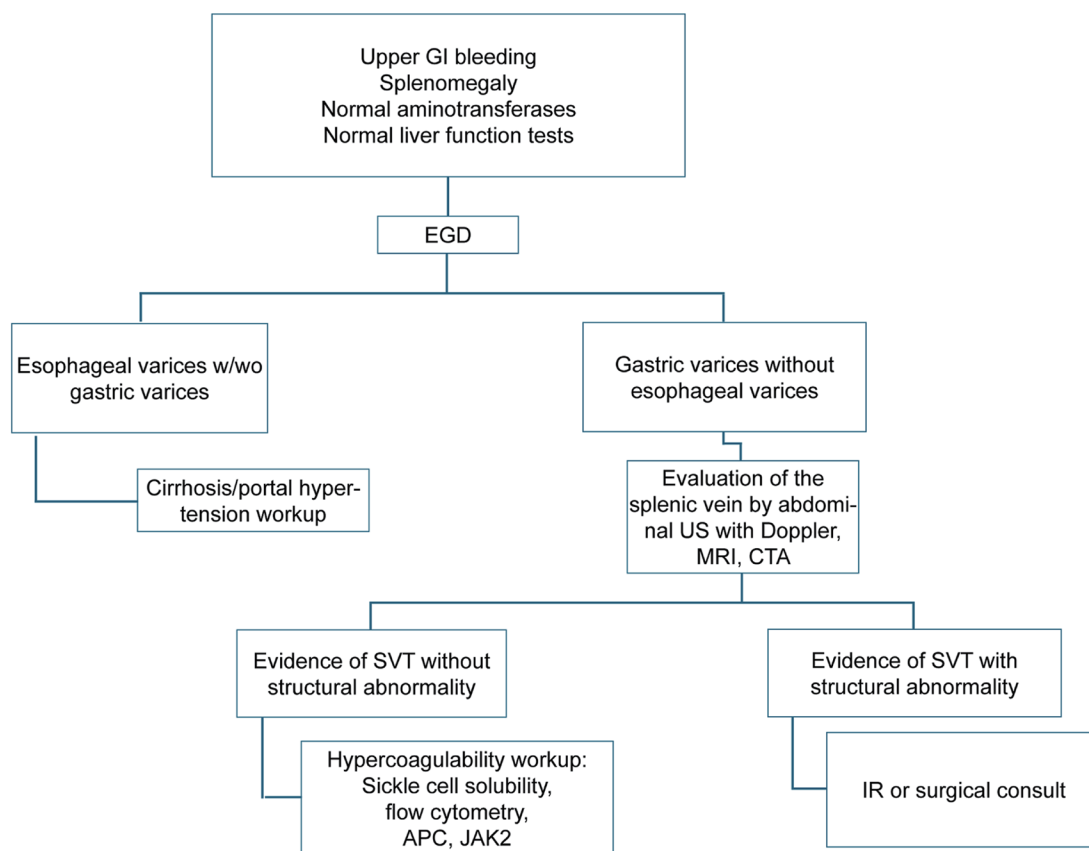
Fig. 2. An algorithm for evaluation and management of SVH. APC, activated protein C; CTA, computed tomography angiography; EGD, esophagogastroduodenoscopy; GI, gastrointestinal; IR, interventional radiology; MRI, magnetic resonance imaging; SVH, splenic venous hypertension; SVT, splenic vein thrombosis; US, ultrasound; w, with; wo, without.

The development of ascites is uncommon due to the absence of portal hypertension and cirrhosis.[1]

Diagnosis

The typical presentation of SVH involves GI bleeding due to gastric varices often in the absence of esophageal varices, splenomegaly with normal aminotransferases, and liver function tests.[1] The etiology of SVH can be determined by imaging. The initial imaging modality typically employed is the transabdominal US with Doppler, although it has limited efficacy in visualizing the SV. US is mainly used to exclude liver cirrhosis and systemic portal hypertension.[64] Contrast-enhanced endoscopic ultrasound (EUS) can be used in cases where other diagnostic modalities have failed to evaluate the patency of the SV. Further characterization of the splenic vasculature by CT angiography or magnetic resonance angiography is possible. These are non-invasive and generally preferred for determining the SV diameter, patency, and presence of thrombosis. While SV angiography can provide more detail, this modality is used infrequently due to its invasive nature. Gastric varices can be detected by various modalities, including CT, MRI, EUS with Doppler, or esophagogastroduodenoscopy (Fig. 2).[1]

Management

The main therapeutic approach for SVH, similar to PVH in-

volves reducing splenic venous pressure by addressing the primary pathological process. In both SVH and PVH, initial steps include hemodynamic stabilization, such as with any GI bleeding which includes adequate volume resuscitation and monitoring of airway, breathing, and circulation. Hemostasis by endoscopic band ligation, methacrylate variceal injection, and/or octreotide infusion are often required.[65] Some reports have shown a benefit of beta blockers in preventing recurrent bleeding.[66] Specific approaches for SVH treatment depend on the mechanism by which SVH occurs (Fig. 2).

Compression Etiologies

The management of SVH resulting from compression of the SV varies based on the etiology. For pancreatic lymphoma, chemotherapy and radiologic monitoring for SV patency and resolution of splenomegaly are recommended.[12,13] In contrast, for pancreatic NETs, Dumont *et al*. found that systemic chemotherapy had no observed impact on SVH, whereas distal pancreatectomy successfully prevented GI bleeding. Based on the data, a complete macroscopic resection of the pancreatic NET by distal pancreatectomy is recommended.[67] For compression due to pancreatic cysts, distal pancreatectomy, and splenectomy have demonstrated good outcomes in patients.[20,68] For peripancreatic lymph node tuberculosis and retroperitoneal fibrosis, splenectomy has been reported to be an effective option, although the data are limited.[23,24] Splenectomy and repair of the defect are recommended for Bochdalek hernia.[18] Splenectomy and aneurysmectomy have

been suggested for SAAs.[15,16,69] Studies on aneurysmectomy alone have not been reported.

Stenosis Etiologies

No large studies have been conducted on managing SV stenosis and SVH. Case reports have shown successful management with splenectomy, which seems to be the best option until data to the contrary are available.[3,27]

Inflammation Etiologies

There is a lack of guidelines regarding the management of SVH in pancreatitis. A study of pancreatitis-induced SVH reported that eleven of the patients underwent splenectomy, two underwent splenic artery embolization, one received endoscopic therapy, and three were managed conservatively. At 29 months, none had recurrent bleeding.[33] A strength of this study was the good statistical power. In the case of AP, where the trigger of the inflammation can be eliminated, after controlling variceal bleeding, it would seem reasonable to observe the effects on SVH and variceal hemorrhage. If bleeding recurs, splenectomy may be required for SVH management. For cases of chronic pancreatitis with fibrotic reaction, splenectomy is more likely to be necessary. However, larger studies on conservative or endovascular management outcomes are needed.

Thrombosis Etiologies

SVT secondary to FVL or PNH should be managed with lifelong anticoagulation.[49,50,54] Additionally, monoclonal antibodies, including eculizumab, have been shown to reduce the risk of hemolysis and thrombosis in PNH.[61,70] A case series of three patients demonstrated that eventual discontinuation of anticoagulation was safe after initiating eculizumab.[71] However, the sample size was small. Randomized trials are needed to determine the safety of discontinuing anticoagulation after initiating eculizumab. On the contrary, reports have shown that conservative management, including rest, analgesia, and hydration, has led to the resolution of symptoms from SV occlusion due to SCT.[51,52,57,72,73] Two gene therapy agents approved by the Federal Drug Administration for sickle cell disease are exagamglogene autotemcel and lovotibeglogene autotemcel, indicated for patients 12 years and older with recurrent vasoactive crises.[74,75] Conservative management is recommended for a first-time episode of SV occlusion. If recurrent episodes occur, gene therapy should be considered.

Wandering spleen is managed by splenopexy if the spleen is still viable and there are no signs of hypersplenism. If SVH persists, splenectomy is recommended.[39,40] Splenectomy and partial splenic embolization have been proposed for PMF.[45,46,47,76] Similarly, resolution of gastric varices has been achieved by partial splenic embolization or gastric devascularization in patients with ET.[43,44] In both PMF and ET, lifelong anticoagulation is recommended.[42,76] However, the risk versus benefit of anticoagulation in the setting of gastric varices needs to be weighed. Once the gastric varices have been managed endoscopically, anticoagulation can be instituted. Hydroxyurea has not been shown to prevent recurrent thrombosis in the SV in PMF.[77] However, the National Comprehensive Cancer Network guidelines recommend hydroxyurea as cytoreductive therapy after one episode of SVT in patients with ET.[78]

Surgically Decreased Splenic Venous Flow Etiologies

There are no large cohort studies on SVH management in PD. Splenectomy is the preferred treatment for symptomatic SVH cases. However, it may not be safe for patients who have un-

dergone complex abdominal surgeries such as PD.[79] Splenic artery embolization is considered a safer option.[80] Tanaka *et al*. studied 118 patients who underwent PD comparing variceal incidence among those with and without SV reconstruction. SV reconstruction decreased the variceal incidence (60% vs. 100%) at six months (p=0.018).[81] The study had a long follow-up period and statistically significant results. Splenic artery embolization is recommended to avoid further surgical complications of splenectomy in these patients. Additionally, SV reconstruction may prevent varix formation.

Prognosis

The prognosis of patients with SVH depends mainly on the primary etiology. Among various etiologies, patients with pancreatic cancer have the worst outcomes due to shorter life expectancy. GI bleeding is relatively rare but the exact incidence is unknown.[1] A retrospective study of 139 SVH patients secondary to pancreatic pathologies was performed. Patients were included if CT or MRI evidenced splenic vein occlusion and if bleeding gastric varices were found on EGD. GI bleeding was present in 15.2% (21/139) of patients; however, no fatalities were reported after 72 months of follow-up.[82] This study included a prolonged follow-up period but had a small sample size.

A retrospective study of 34 patients with chronic pancreatitis and SVH was performed. There were 28 men and six women with a mean age of 36. SV thrombosis was diagnosed on CT or MRI. GI bleeding was defined as bleeding gastric varices seen on EGD excluding all other causes of bleeding. GI bleeding occurred in 15% of patients but no fatalities were reported at four years follow-up.[83] Non-variceal causes of upper GI bleeding were excluded and follow-up was prolonged period but the sample size was small.

Conclusion

Although SVH is rare, it should be considered in cases of variceal bleeding in the absence of liver disease and with gastric varices in the absence of esophageal varices. The primary cause of SVH is increased pressure due to SV obstruction from stenosis, compression, inflammation, thrombosis, or surgically decreased splenic venous flow. Anatomic anomalies, compression due to neighboring mass effect, endothelial dysfunction causing inflammation, and increased coagulopathy causing thrombosis all contribute to underlying SV obstruction. Each of these etiologies leads to a backward pressure flow into collateral circulation, increasing pressure and dilation of gastric fundus veins with increased risk of varices and upper GI bleeding. Successful management and a favorable prognosis depend on selecting the appropriate treatment based on the underlying etiology. In non-malignant etiologies, the reduction of SVH is typically associated with a good outcome.

Further research directions are likely to focus on improved non-invasive diagnostic modalities, less invasive surgical techniques, and non-surgical management options.

Conflict of interest

GYW has been an Editor-in-Chief of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflicts of interest related to this publication.

Author contributions

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