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.

Introduction

Splenic venous hypertension (SVH) or left-sided portal hypertension is a rare condition that presents with upper gastrointestinal bleeding (UGIB) 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 dilatation 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 gastrointestinal bleeding, splenomegaly, and unremarkable liver enzymes and function tests.2

The terms left-sided portal hypertension or splenorenal 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 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

Inflammation

Inflammation is the most common mechanism of SVH and is attributed to the proximity of the SV and pancreatitis in which autodigestion 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 thrombus formation 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 pancreateoduodenectomy (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).12,13

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): SAs 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 splenoectomy. 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).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 peri-pancreatic 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

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Prevalence</th>
<th>Gender Difference</th>
<th>Mean Age</th>
<th>Presentation</th>
<th>Means of Diagnosis</th>
<th>Therapy</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Compression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic NET</td>
<td>1–2% of all pancreatic tumors</td>
<td>N/I</td>
<td>N/I</td>
<td>Abdominal pain, symptoms based on hormone produced</td>
<td>CT, MRI, EUS</td>
<td>Systemic chemotherapy, surgical resection</td>
<td>N/I</td>
<td>N/I</td>
<td>9</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>N/I</td>
<td>N/I</td>
<td>N/I</td>
<td>Lymphadenopathy, B symptoms, symptoms based on the type of lymphoma</td>
<td>Tissue biopsy</td>
<td>Chemotherapy</td>
<td>N/I</td>
<td>N/I</td>
<td>25</td>
</tr>
<tr>
<td>SAA</td>
<td>0.77% of all abdominal aneurysms</td>
<td>N/I</td>
<td>N/I</td>
<td>Epigastric or left upper quadrant pain that radiates to the left shoulder</td>
<td>CT, MRI, contrast angiography, endoscopic US</td>
<td>Surgical excision of aneurysm and/or splenectomy</td>
<td>N/I</td>
<td>N/I</td>
<td>14</td>
</tr>
<tr>
<td>Bochdalek hernia</td>
<td>0.17%</td>
<td>N/I</td>
<td>N/I</td>
<td>Abdominal pain</td>
<td>US, chest x-ray, and CT abdomen</td>
<td>Surgical repair of the defect</td>
<td>N/I</td>
<td>N/I</td>
<td>17,18</td>
</tr>
<tr>
<td>Pancreatic cysts and pseudocysts</td>
<td>14.6–48.1%</td>
<td>N/I</td>
<td>N/I</td>
<td>Abdominal pain, back pain, weight loss, jaundice, and/or palpable mass</td>
<td>CT, MRI, endoscopic US</td>
<td>Distal pancreatectomy and splenectomy</td>
<td>N/I</td>
<td>N/I</td>
<td>20,19</td>
</tr>
<tr>
<td>RF</td>
<td>0.000013%</td>
<td>3:1 male:female ratio</td>
<td>64</td>
<td>Abdominal pain, flank pain, discomfort</td>
<td>CT Abdomen</td>
<td>Splenectomy</td>
<td>N/I</td>
<td>N/I</td>
<td>22</td>
</tr>
<tr>
<td>Peripancreatic lymph node tuberculosis</td>
<td>N/I</td>
<td>N/I</td>
<td>N/I</td>
<td>Abdominal pain and biliary obstruction</td>
<td>CT abdomen, Ziehl-Neelsen staining</td>
<td>N/I</td>
<td>N/I</td>
<td>N/I</td>
<td>24</td>
</tr>
<tr>
<td><strong>B. Stenosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic splenic vein stenosis</td>
<td>N/I</td>
<td>N/I</td>
<td>N/I</td>
<td></td>
<td>CT abdomen</td>
<td>Splenectomy</td>
<td>N/I</td>
<td>N/I</td>
<td>3</td>
</tr>
<tr>
<td><strong>C. Inflammation</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Pancreatitis</td>
<td>15%</td>
<td>Male predominant</td>
<td>N/I</td>
<td>Abdominal pain, gastrointestinal bleeding</td>
<td>CT abdomen</td>
<td>Splenectomy</td>
<td>N/I</td>
<td>N/I</td>
<td>34,32</td>
</tr>
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</table>

(continued)
### D. Thrombosis

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

### E. Surgically Decreased Splenic Venous Flow

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

CBC, complete blood count; CT, computed tomography; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; ET, essential thrombocytemia; 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

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

#### B. Stenosis

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

#### C. Inflammation

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number of cases</th>
<th>Mean Age</th>
<th>Presentation</th>
<th>Means of Diagnosis</th>
<th>Therapy</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>3</td>
<td>54</td>
<td>Abdominal pain, GI bleeding (melena, hematemesis)</td>
<td>CT abdomen, MRI abdomen</td>
<td>Splenectomy, splenic artery embolization</td>
<td>Resolution of GI bleeding</td>
<td>29 months</td>
<td>30,32,33</td>
</tr>
</tbody>
</table>
Table 2. (continued)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number of cases</th>
<th>Presentation</th>
<th>Mean Age</th>
<th>Means of Diagnosis</th>
<th>Therapy</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic cancer</td>
<td>3</td>
<td>Abdominal pain (quadrant, epigastrium)</td>
<td>50</td>
<td>CT abdomen/pelvis</td>
<td>Distal pancreatectomy and splenectomy</td>
<td>Resolved portal hypertensive gastropathy</td>
<td>N/I</td>
<td>36–38</td>
</tr>
<tr>
<td>Wandering spleen</td>
<td>3</td>
<td>Lower abdominal pain, GI bleeding</td>
<td>74</td>
<td>Abdominal US, CT abdomen/pelvis</td>
<td>Splenic vein thrombectomy and splenectomy</td>
<td>Splenic artery embolization</td>
<td>2 lost to follow up, 1 comfort measure/death</td>
<td>39–41</td>
</tr>
<tr>
<td>ET</td>
<td>2</td>
<td>Upper GI bleeding (melena), abdominal pain</td>
<td>55.6</td>
<td>CT abdomen, venogram, CT abdomen</td>
<td>Splenic artery embolization, transgastric partial splenectomy</td>
<td>Resolution of bleeding and varices</td>
<td>3 months</td>
<td>43,44</td>
</tr>
<tr>
<td>PMF</td>
<td>3</td>
<td>Upper GI bleeding (hematemesis, melena), fatigue</td>
<td>57.6</td>
<td>CT abdomen, bone marrow biopsy</td>
<td>IV heparin</td>
<td>Resolution of bleeding and varices on EGD</td>
<td>36 months</td>
<td>1, 5, 14, 49, 50</td>
</tr>
<tr>
<td>FVL</td>
<td>2</td>
<td>Abdominal pain, weight loss</td>
<td>50</td>
<td>CT abdomen, hypercoagulable workup</td>
<td>Conservative management, splenic artery embolization</td>
<td>Resolution of bleeding</td>
<td>1, 5, 14, 49, 50</td>
<td></td>
</tr>
<tr>
<td>SCT</td>
<td>3</td>
<td>Abdominal pain, vomiting</td>
<td>25.5</td>
<td>CT abdomen, hemoglobin electrophoresis</td>
<td>CT abdomen, CTA, CT, CT</td>
<td>Resolution of varices and bleeding on EGD</td>
<td>N/I</td>
<td>51, 52, 57</td>
</tr>
<tr>
<td>PMH</td>
<td>3</td>
<td>Abdominal pain, dark urine</td>
<td>38</td>
<td>CT abdomen, flow cytometry</td>
<td>IV heparin followed by oral anticoagulation, eculizumab</td>
<td>Reduction of intravascular hemolysis</td>
<td>3 months</td>
<td>54, 55, 58</td>
</tr>
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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; SCL, splenic cell leukemia; SFT, solitary fibrous tumor; US, ultrasound.
Tidwell J. et al: Left-sided portal hypertension

Stenosis
Idiopathic SV stenosis: Few cases of SV stenosis have been reported; therefore, the exact incidence is unknown. The reported 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-
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 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 portosplenic enteric 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, with 68% detected one week 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. 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 limitations included a lack of endoscopic data and consecutive follow-up.

Thrombosis

Pancreatic cancer: Solid pseudopapillary tumors of the pancreas are rare, accounting for approximately 3% of pancreatic tumors.32 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 hyperechoic 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.33 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. SVH 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 variable 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 peri-gastric 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 acti-
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 hematemia, 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 hematemia, 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 splanchic 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 splanchic 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 209:247. 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. SVP+SA (n=227) included those with division of the SV and preservation of the SA. SVP+SR (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 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 SVP+SR group, 37% in the SVP group, and 41.6% in the SV-SMV/LRV 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/LRV 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).56,60,61

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 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
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 involves 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

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**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.
been suggested for SAAs. Studies on aneurysmectomy is still viable and there are no signs of hypersplenism. If is recommended for a first-time episode of SV occlusion. If is managed endoscopically, anticoagulation can be included. Hydroxyurea has not been shown to prevent re-bleeding recurs, splenectomy may be required for SVH management. For cases of chronic pancreatitis with fibrotic reaction, splenectomy may be more likely to be necessary. However, others have managed conservatively. It is worth weighing the gastric varices needs to be weighed. Once the gastric varices and dilation of gastric fundus veins with increased risk of hydroxyurea causing thrombosis all contribute to underlying

**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 splenecy and embolization, one received endoscopic therapy, and three were managed conservatively. At 29 months, none had recurrent bleeding. 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 control of 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 may be necessary. However, large studies on conservative or endovascular management outcomes are needed.

**Thrombosis Etiologies**

SVT secondary to FVL or PNH should be managed with lifelong anticoagulation. Additionally, monoclonal antibodies, including eculizumab, have been shown to reduce the risk of hemolysis and thrombosis in PNH. A case series of three patients demonstrated that eventual discontinuation of anticoagulation was safe after initiating eculizumab. 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. 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. 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 splenectomy if the spleen is still viable and there are no signs of hypersplenism. If SVH persists, splenectomy is recommended. Partial splenic embolization has been proposed for PMF. Similarly, resolution of gastric varices has been achieved by partial splenic embolization or gastric devascularization in patients with ET. In both PMF and ET, lifelong anticoagulation is recommended. 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. However, the National Comprehensive Cancer Network guidelines recommend hydroxyurea as cytoreductive therapy after one episode of SVT in patients with ET.

**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 undergone complex abdominal surgeries such as PD. Splenic artery embolization is considered a safer option. 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). 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. 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. 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 26 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. Non-variceal causes of upper GI bleeding were excluded and follow-up was prolonged 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.

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**Conflict of interest**

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References


