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GUIDELINES

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Guidelines for the diagnosis and treatment of idiopathic portal hypertension, extrahepatic portal obstruction, and Budd–Chiari syndrome in Japan

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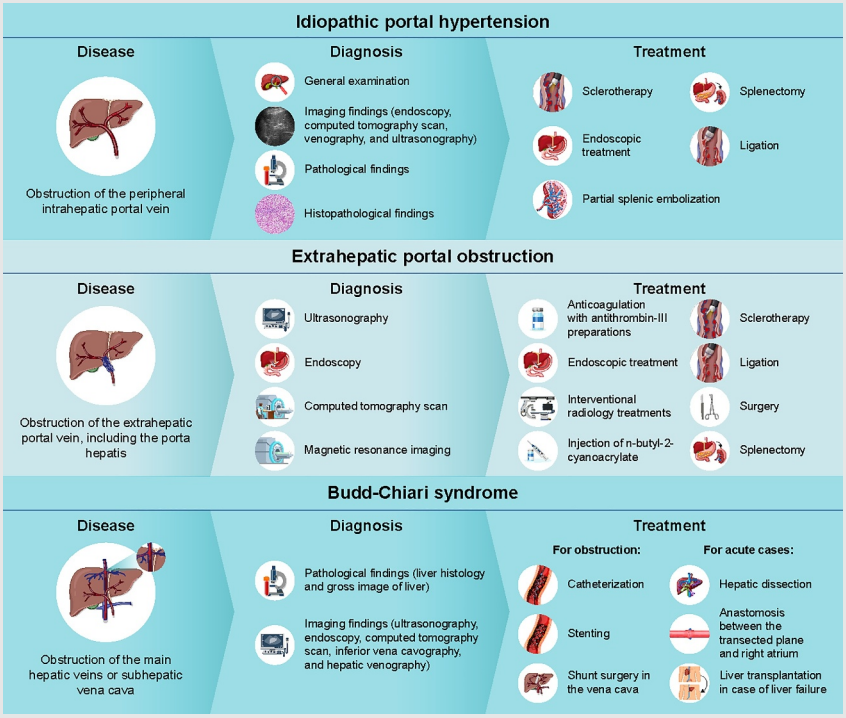
Graphical Abstract



This is the English version of the guidelines for the diagnosis and treatment of idiopathic portal hypertension, extrahepatic portal obstruction, and Budd–Chiari syndrome, which were established and revised in 2018 by the Aberrant Portal

Abbreviations: BCS, Budd–Chiari syndrome; EHO, extrahepatic portal obstruction; IPH, idiopathic portal hypertension; IVR, interventional radiology; NBCA, n-butyl-2-cyanoacrylate; PSE, partial splenic embolization.

Hemodynamics Study Group under the jurisdiction of the Ministry of Health, Labor, and Welfare in Japan.

Abstract

This is the English version of the guidelines for the diagnosis and treatment of idiopathic portal hypertension, extrahepatic portal obstruction, and Budd–Chiari syndrome, which were established and revised in 2018 by the Aberrant Portal Hemodynamics Study Group under the jurisdiction of the Ministry of Health, Labor, and Welfare in Japan. These guidelines are excerpts, and the full version consists of 86 clinical questions and explanations, totaling 183 pages in Japanese.

KEYWORDS

Budd–Chiari syndrome, extrahepatic portal obstruction, idiopathic portal hypertension, portal hypertension

INTRODUCTION

A research group focusing on idiopathic portal hypertension (IPH), under the jurisdiction of the Ministry of Health and Welfare (currently the Ministry of Health, Labor, and Welfare), was established in Japan in 1975, and has been conducting ongoing and multidisciplinary research investigations for nearly 50 years. In 1984, extrahepatic portal obstruction (EHO) and Budd–Chiari syndrome (BCS) were added to the list of diseases to be studied, and an Aberrant Portal Hemodynamics Study Group was formed. In 2001, the Diagnosis and Treatment methods for Aberrant Portal Hemodynamics were established, and in 2007, they were revised into the Guidelines for the Diagnosis and Treatment of Aberrant Portal Hemodynamics. After another revision of the 2013 version, it was published in 2017 as the world's first guideline for aberrant portal hemodynamics in an English-language journal.[1] After further revisions, the 2018 guidelines, which complied with the Minds Guidelines, were published. The present manuscript is part of the 2018 edition of the guidelines with additional clinical questions (CQs). The full version comprises 86 CQs and explanations, totaling 183 pages. These CQs in this manuscript were extracted through collaboration between the guideline development committee and the systematic review team. Moreover, the approval of an external evaluation committee has been obtained.

After the evaluation of the evidence prepared by the systematic review team, the guideline development committee drafted recommendations for each CQ. The committee carefully considered the balance between benefits and risks associated with these recommendations. The strength of evidence was determined as follows in accordance with Minds guideline: A. Strong; B. Moderate; C. Weak; and D. Very Weak (Table S1). The strength of recommendation was as follows: 1. Strong Recommendation to "implement" or "not implement," and 2. Weak Recommendation to "implement" or "not implement." For a recommendation to be implemented, it required at least a 70% affirmative vote.

DIAGNOSTIC AND TREATMENT GUIDELINES FOR IPH

Disease concept and symptoms

IPH is a disease of unknown etiology in which obstruction or stenosis of the branches of the peripheral intrahepatic portal vein leads to portal hypertension. Depending on the severity of the disease, symptoms include esophagogastric varices, ectopic varices, portal hypertensive gastropathy, ascites, hepatic encephalopathy, splenomegaly, anemia, liver dysfunction, and bleeding tendencies (Table 1). In typical cases, this pathology does not lead to cirrhosis and has a relatively favorable prognosis, as it is unlikely to become a risk factor for hepatocellular carcinoma.

In 1883, Banti reported a disease of unknown etiology that had no apparent cause, as in cases of cirrhosis, but produced marked splenomegaly and portal hypertension. The pathological feature of the disease was fibrosis in the spleen, which was named Banti's disease. In 1967, Boyer et al. reported a condition of unknown etiology that occurred in Banti's disease, and was characterized by elevated portal venous pressure and marked splenomegaly, but no evidence of liver cirrhosis, establishing the concept of IPH. In Western countries, IPH is recognized as a type of idiopathic noncirrhotic portal hypertension, which is defined as portal hypertension of unknown etiology with no apparent development in the liver.[2]

Etiology/pathophysiology

The cause of idiopathic noncirrhotic portal hypertension remains unknown; however, several theories have been proposed, including intrahepatic peripheral portal vein thrombosis, splenogenesis, and autoimmune abnormalities. This condition is more common in middle-aged women, and autoimmune abnormalities are thought to be the etiology of the disease. Serological tests show features similar

TABLE 1 Clinical findings (national epidemiological surveys).

Characteristics		1999 survey	2005 survey	2015 survey
IPH		(*n* = 169)	(*n* = 89)	(*n* = 279)
Sex	Male	40/167 (24)	24 (27)	83 (30)
Age (years)	Mean ± SD	49.5 ± 16.4	48.6 ± 16.7	47.0 ± 19.1
Duration from symptom onset (years)	Mean ± SD	3.6 ± 7.0	2.4 ± 5.5	1.7 ± 4.0
Clinical symptoms				
Esophageal varices	Present	139/162 (86)	73/84 (87)	184/233 (79)
Gastric varices	Present	73/152 (48)	44/79 (56)	95/229 (41)
Ascites	Present	18/169 (11)	12/78 (15)	39/236 (17)
Splenomegaly	Present	133/169 (79)	70/78 (90)	202/228 (89)
Anemia	Present	72/169 (43)	40/74 (54)	145/226 (64)
Gastrointestinal bleeding	Present	57/153 (37)	25/81 (31)	85/247 (34)
Hepatic encephalopathy	Present	12/169 (7)	1/79 (1)	9/239 (4)
EHO		(*n* = 97)	(*n* = 70)	(*n* = 211)
Sex	Male	52 (54)	45 (51)	113 (54)
Age (years)	Mean ± SD	37.6 ± 23.9	32.7 ± 26.2	33.1 ± 24.9
Duration from symptom onset (years)	Mean ± SD	2.4 ± 6.2	1.4 ± 3.0	1.8 ± 5.7
Clinical symptoms				
Esophageal varices	Present	69/92 (75)	43/65 (66)	110/164 (67)
Gastric varices	Present	37/90 (41)	31/64 (48)	78/155 (50)
Ascites	Present	18 (19)	17/67 (25)	33/178 (19)
Splenomegaly	Present	56 (58)	42/68 (62)	107/170 (63)
Anemia	Present	33 (34)	37/62 (60)	90/159 (57)
Gastrointestinal bleeding	Present	42/87 (48)	30/69 (43)	67/191 (35)
Hepatic encephalopathy	Present	4 (4)	2/67 (3)	6/179 (3)
BCS		(*n* = 44)	(*n* = 33)	(*n* = 112)
Sex	Male	17 (39)	19 (22)	67 (60)
Age (years)	Mean ± SD	48.6 ± 18.5	41.7 ± 16.8	40.5 ± 16.0
Duration from symptom onset (years)	Mean ± SD	2.0 ± 3.6	1.6 ± 2.6	1.5 ± 3.9
Clinical symptoms				
Esophageal varices	Present	36/41 (88)	21/29 (72)	52/91 (57)
Gastric varices	Present	9/40 (23)	7/28 (25)	21/90 (23)
Ascites	Present	11/43 (26)	13/31 (42)	41/99 (41)
Splenomegaly	Present	22/43 (51)	23/29 (79)	59/93 (63)
Anemia	Present	6/43 (14)	4/30 (13)	34/88 (39)
Gastrointestinal bleeding	Present	4/38 (11)	2/29 (7)	12/105 (11)
Hepatic encephalopathy	Present	0/44 (0)	3/30 (10)	8/105 (8)

Note: The percentages are shown in parentheses.

Abbreviations: BCS, Budd–Chiari syndrome; EHO, extrahepatic portal obstruction; SD, standard deviation.

Modified from Ohfuji et al.[5] with permission.

to those of autoimmune diseases that are frequently complicated by autoimmune conditions.

Portal vein hemodynamics are characterized by a marked increase in the splenic blood flow. Portal venous blood flow is thereby increased to 2–2.5-fold the normal level. The proliferation of venous sinus endothelial cells (pestle cells) in the red splenic cord causes splenomegaly, with a disorganized arrangement of the pestle cells and irregular widening of the intervening slits between them due to excess production of nitric oxide.[3] Blood from the splenic artery passes through the slits as it migrates into the splenic vein, and dilation of the slits is thought to attenuate vascular resistance, thereby contributing to increased splenic blood flow. Narrowing and obstruction of the peripheral branches of the portal vein are observed in the liver. Thus, it is thought that increased portal venous blood flow associated with increased splenic blood flow and increased intrahepatic portal vascular resistance due to fibrosis around the portal vein combine to cause increased portal venous pressure.[4]

Epidemiology

In the 2015 National Epidemiologic Survey, the estimated annual number of patients with IPH was 1000 (95% confidence interval [CI] 810–1300). The male-to-female ratio was approximately 0.43:1, with a prevalence of 7.9 per million people. In the 2005 National Epidemiologic Survey, the estimated annual number of patients was 850 (95% CI 640–1070), a slight increase from the previous decade. However, in the 1999 survey, the number was 920 (95% CI 710–1140), suggesting no significant change over the past 20 years.[5] The mean age at the time of the confirmed diagnosis was 47.0 years. Regarding regional characteristics, the disease is somewhat more prevalent in the Hokkaido, Tohoku, and Kanto regions.

Pathological findings

Gross image of the liver: In the early stage, there is mild fibrosis in the portal area, and sclerosis of the intrahepatic portal branches. In the middle stage, atrophy of the liver parenchyma in the subhepatic capsular region becomes prominent. Wrinkles are observed on the liver surface, and an abnormal approximation of the branches of the medium and large portal veins to the hepatic capsule is observed. Sclerosis and thrombi of portal branches are often observed in the large portal vein. In later stages of the disease, atrophy can be severe, with extreme atrophy of the right or left lobe in some cases.

Liver histology: Collapsed or narrowed peripheral portal branches and systemic sclerosis of the portal branches are observed. Fibrosis is present in the portal area, often with round fibrous enlargement. Thrombosis of the organizing process occurs heterogeneously at various levels in the intrahepatic and extrahepatic portal branches. Abnormally dilated thin-walled vessels, known as aberrant blood vessels, are observed near the peripheral portal area.[6] Hyperplastic nodules, such as nodular regenerative hyperplasia and focal nodular hyperplasia, are frequently observed in the liver.

Gross image of the spleen: In addition to marked splenomegaly, dilatation of the splenic arterioles and occasional concomitant splenic artery aneurysms have been reported.

Splenic histology: Hyperplasia of fine reticular fibers around the splenic artery branches and irregular hyperplasia of the capillary endothelial cells in the red pulp that comprise the splenic sinus are clearly observed.[7] Gaps (slits) between endothelial cells are thought to open irregularly, thus decreasing blood flow resistance, and increasing blood flow to the splenic sinus.[8]

CQ 1. Is liver biopsy useful in the diagnosis of IPH?

Statement: Histopathological findings specific to the liver in IPH have not been clarified, but they are characteristic. Therefore, liver biopsy for IPH is useful for ruling out other diseases. This CQ corresponds to IPH CQ A-1 in the Japanese version.

Recommendation level: Weak recommendation (100% consensus rate).

Level of evidence: C (Low).

Hematological findings

Peripheral blood tests show decreased levels of one or more blood cell components. The decrease in the platelet count is particularly marked. Liver function test results are often mildly abnormal.

Imaging findings

Ultrasonography

The surface of the liver is often smooth; however, in some cases, it shows large protrusions, depressions, and an overall wavy appearance[9] (Figure 1). Ultrasound Doppler examination reveals markedly increased portal and splenic venous blood flow. Second, a thrombus may be observed in the portal vein. Elasticity measurements using ultrasound elastography show a mild increase in liver hardness and a marked increase in splenic hardness.[10]

Computed tomography scan and hepatic venography

As the intrahepatic portal venous circulation is impaired, resulting in atrophy and compensatory central enlargement of the hepatic parenchyma in the subhepatic capsule region, large portal and hepatic venous branches run close to the liver surface (Figure 2). The

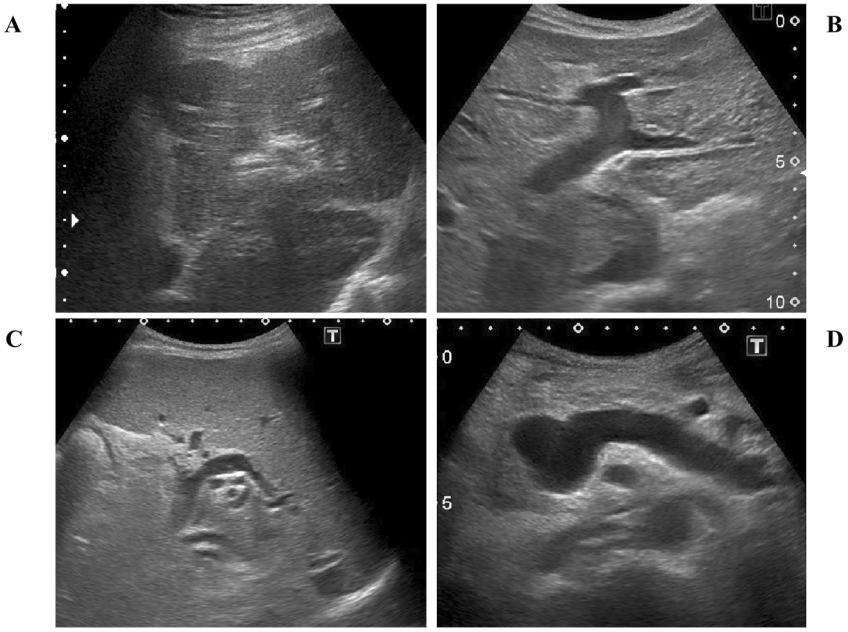


FIGURE 1 Abdominal ultrasound images in a patient with idiopathic portal hypertension. (A) Epigastric longitudinal scan shows the rippled edge of the left lobe of the liver. (B) Transverse scan of the epigastric area shows a slightly coarsened internal echo in the left lobe of the liver. (C) Subcostal scan of the left costal arch shows splenomegaly. (D) Transverse scan of epigastric area shows an enlarged splenic vein.

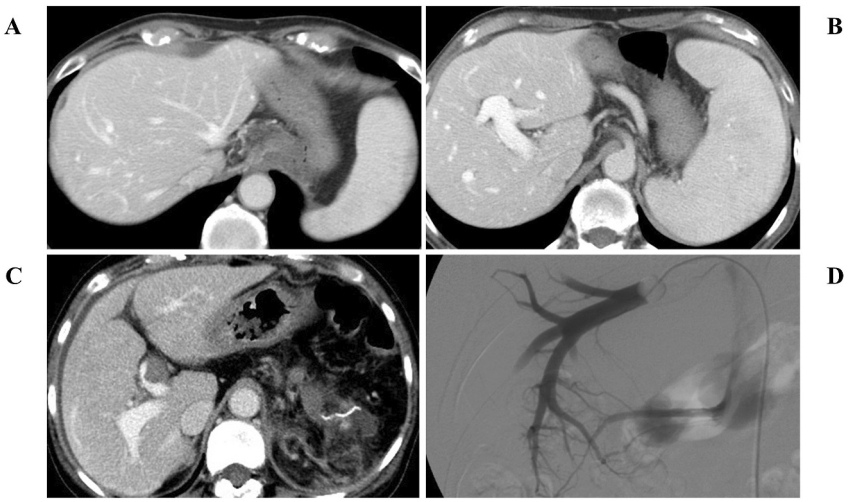


FIGURE 2 Contrast-enhanced computed tomography (CT) images of the abdomen and hepatic venography. (A) Contrast-enhanced portal phase CT. The portal vein approaches the hepatic surface as a result of atrophy of the hepatic parenchyma in the subcapsular area. (B) Contrast-enhanced CT in the portal phase. The thick right portal vein runs close to the hepatic surface due to compensatory central enlargement. (C) Portal phase contrast-enhanced CT showing the peripheral portal vein running near the surface of the right lobe of the liver and thrombus in the left branch of the portal vein. (D) Hepatic venography shows anastomosis between veins and weeping willow-like changes.

hypoperfusion zone of the portal vein under the hepatic capsule may be observed as a pale contrast-enhanced area in the early arterial phase as a result of compensatory hepatic arterial blood flow.[11] Hepatic venography often shows anastomosis between hepatic vein branches, namely a "weeping willow-like" appearance. Wedge hepatic venous pressure is either normal or mildly elevated.

Endoscopy

Varices are often found in the esophagus and stomach (Figure 3). Portal hypertensive gastroenteropathy and ectopic varices in the duodenum, peri-bile ducts, and lower gastrointestinal tract are occasionally observed.

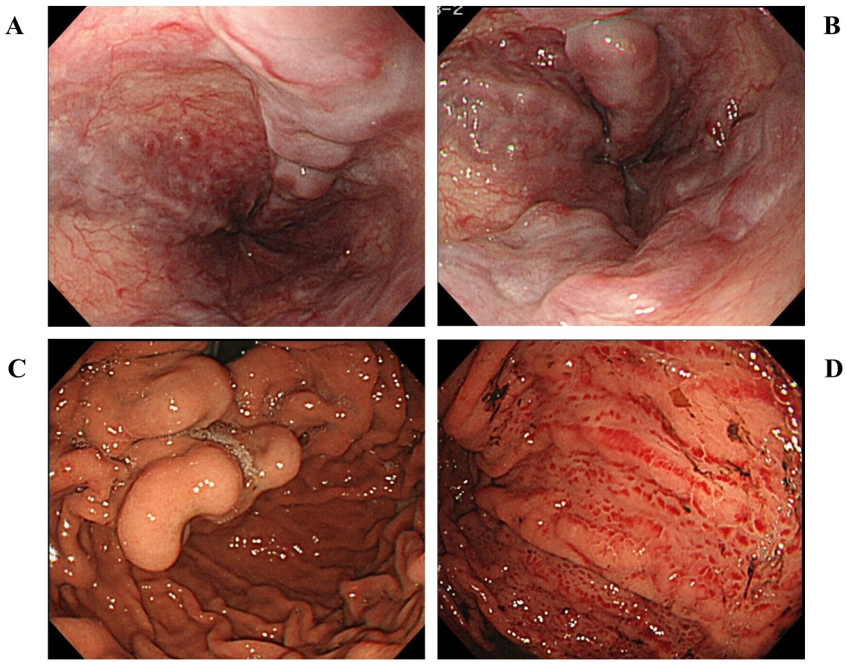


FIGURE 3 Endoscopic findings of the upper gastrointestinal tract. (A) Moderately enlarged, beady (F2) varices are observed in the upper and middle esophagus (Ls, F2, Cb, RC2). (B) Multiple F2 varices are observed in the lower esophagus (Li, F2, Cb, RC1). (C) F2 varices are observed in the gastric fundus (Lg-f, F2, Cw, RC0). (D) Severe portal hypertensive gastropathy with hematin due to diffuse hemorrhage in the gastric fundus.

CQ 2. Is angiography useful in the diagnosis of IPH?

Statement: IPH is known to cause characteristic changes in the portal and hepatic veins, and angiography is useful in capturing these features. This CQ corresponds to IPH CQ B-2-4 in the Japanese version.

Recommendation level: Weak recommendation (100% consensus rate).

Level of evidence: D (Very low).

Method of diagnosis

Because this pathology is recognized as a syndrome and the pathophysiology varies with the disease stage, a comprehensive diagnosis should be made based on general examination, imaging, and pathological findings. A definitive diagnosis should ideally be supported by the histopathological findings of the liver. Diseases that should be excluded from the diagnosis include cirrhosis, EHO, BCS, hematologic diseases, parasitic diseases, granulomatous liver disease, congenital liver fibrosis, chronic viral hepatitis, and primary cholestatic cholangitis in the noncirrhotic phase.

Treatment

Currently, there are no fundamental therapies for the treatment of IPH. Variceal bleeding is the most important prognostic factor. Endoscopic hemostasis (sclerotherapy and ligation) is performed in cases of bleeding, and emergency surgery is considered when this approach fails to achieve hemostasis. Endoscopic treatment or surgery should be considered for bleeding esophageal and gastric varices, even in prophylactic cases in which bleeding has not yet occurred.[12,13] Refractory esophagogastric varices with recurrent bleeding or recurrence are often associated with splenomegaly and hypersplenism (pancytopenia), and the effectiveness of procedures for devascularization of the lower esophagus and upper stomach with splenectomy (Hassab's operation) and partial splenic embolization (PSE) has been reported.[14] The treatment strategies for esophagogastric varices, ectopic varices, and splenomegaly/hypersplenism are listed in Table 2.

TABLE 2 Treatment strategies for esophagogastric varices, ectopic varices, and splenomegaly/hypersplenism.

Esophageal varices	
1	Patients with bleeding from esophageal varices should be managed symptomatically with general measures for hemorrhagic shock and balloon tamponade, and endoscopic treatment, such as endoscopic injection sclerotherapy and endoscopic variceal ligation, should be performed as soon as possible. If hemostasis is not achieved even with the above treatments, emergency surgery should be considered
2	In cases where temporary hemostasis is achieved after the patient's condition improves, continuation of endoscopic treatment, elective surgery, or a combination of both should be considered
3	In cases with no bleeding, endoscopic treatment, prophylactic surgery, or a combination of both should be considered based on endoscopic findings of the esophagus
4	As a stand-alone surgical treatment, a "direct interruption procedure", such as esophageal transection or devascularization of the lower esophagus and upper stomach with splenectomy, or a "selective shunt procedure" should be considered. As a combination therapy with endoscopic treatment, "devascularization of the lower esophagus and upper stomach with splenectomy (Hassab's operation)" should be considered
Gastric varices	
1	Gastric varices in the cardia that are contiguous with esophageal varices should be treated according to the treatment strategy for esophageal varices described above
2	Patients with bleeding from isolated gastric varices should be managed symptomatically with general measures for hemorrhagic shock, balloon tamponade, etc., and treated endoscopically as soon as possible. If hemostasis is not achieved even with the above treatments, IVR such as BRTO, or emergency surgery, should be considered
3	After hemostasis is achieved and the patient's condition improves, continued endoscopic treatment, IVR such as BRTO, or elective surgery (Hassab's operation) should be considered
4	In cases with no bleeding, endoscopic treatment, IVR, or prophylactic surgery should be considered based on endoscopic findings of the stomach
5	As a surgical treatment, devascularization of the lower esophagus and upper stomach with splenectomy (Hassab's operation) should be considered
Ectopic varices	
1	Patients with bleeding from ectopic varices should be managed symptomatically with general measures for hemorrhagic shock and treated endoscopically as soon as possible. If hemostasis is not achieved even with the above treatments, IVR or emergency surgery should be considered
2	In cases where temporary hemostasis is achieved after the patient's condition improves, continued endoscopic treatment, IVR, or elective surgery should be considered
3	In cases with no bleeding, endoscopic treatment, IVR, or prophylactic surgery should be considered based on endoscopic findings
Splenomegaly and hypersplenism	
1	When symptoms (pain, compression) associated with a large spleen are prominent, or when there are complications, such as bleeding tendency due to severe thrombocytopenia (platelets $<5 \times 10^4/mm^3$, white blood cells $<3000/mm^3$, or red blood cells $<300 \times 10^4/mm^3$) that is caused by splenomegaly, partial splenic embolization or splenectomy should be considered if the medical treatment is difficult

Abbreviations: BRTO, balloon-occluded retrograde transvenous obliteration; IVR, interventional radiology.

CQ 3. Which is more effective in treating esophageal and gastric varices in IPH, surgical or endoscopic therapy? Additionally, is splenectomy effective?

Statement: The most important prognostic factor in IPH is esophageal variceal bleeding. Cases involving bleeding should be treated endoscopically with hemostasis. Prophylactic endoscopic treatment is also indicated. Refractory esophageal varices that rebleed or recur are often associated with splenomegaly and hypersplenism (pancytopenia), which are characteristic of IPH and portosystemic shunt with a large amount of blood flow. In these cases, splenectomy, direct interruption procedures, such as devascularization of the lower esophagus and upper stomach with splenectomy (Hassab's operation), and the selective shunt procedure should also be considered. This CQ corresponds to IPH CQ D-1 in the Japanese version.

Recommendation level: Weak recommendation (100% consensus rate).

Level of evidence: D (Very low).

CQ 4. Is PSE effective as adjunctive therapy in IPH?

Statement: PSE has been reported to be effective for esophageal and gastric varices, pancytopenia, splenomegaly, and splenic artery aneurysm (common as an accompanying lesion) in IPH. This CQ corresponds to IPH CQ F-6 in the Japanese version.

Recommendation level: Weak recommendation (100% consensus rate).

Level of evidence: C (Low).

Severity classifications

Male sex, onset at a young age, complications of esophageal and gastric varices, ascites, portal vein thrombosis, human immunodeficiency virus infection, hepatic atrophy, and liver failure are associated with the severity of the disease.[13,15,16] The severity classifications for Japan are listed in Table 3.[17,18] Public funds are available for patients showing symptoms of severity at III or more.

Prognosis

The 10-year survival rate is favorable at 73%–90%[13,19], and the leading causes of death are bacterial infection (30%), liver failure (25%), and variceal hemorrhage (17%).[20] Regarding prognostic factors, treatment of esophageal varices has been shown to improve prognosis, and the presence of hepatic encephalopathy at diagnosis is a poor prognostic factor.[16]

TABLE 3 Severity classifications of idiopathic portal hypertension, extrahepatic portal obstruction, and Budd–Chiari syndrome.

Factors/severity	I	II	III	IV	V
Esophageal, gastric, and ectopic varices	–	+	+ +	+ + +	+ + +
Portal hypertensive findings	–	+	+ +	+ +	+ +
Physical activity restriction	–	–	+	+ +	+ +
Gastrointestinal bleeding	–	–	–	–	+
Liver failure	–	–	–	–	+

Note: Esophageal, gastric, and ectopic varices: (+) varices present, but not hemorrhagic; (++) easily bleeding varices, but no history of bleeding. Easily bleeding esophageal/gastric varices are those with F2 or larger, or those with a red color sign regardless of the F factor, according to the general rules for recording endoscopic findings of esophagogastric varices (The Japan Society for Portal Hypertension)[17]. Therefore, ectopic varices should be treated accordingly; (+++) varices that bled easily and had a history of bleeding. Therefore, ectopic varices should be treated accordingly. Portal hypertensive findings: (+) one or more portal hypertensive gastroenteropathy, ascites, bleeding tendency, splenomegaly, and anemia are present, but do not require treatment; (++) one or more of the above findings requires treatment. Physical activity restriction: (+) the patient experienced restricted physical activity due to these three diseases, but could walk and care for themself, and was awake at least 50% of the day; (++) the patient requires assistance as a result of physical activity limitations caused by these three diseases and stays in bed at least 50% of the day. Gastrointestinal bleeding: (+) the patient currently has active or refractory gastrointestinal bleeding. Liver failure: (+) signs of hepatic failure are a serum total bilirubin level of 3 mg/dl or higher and hepatic coma level II or higher (Japan Society of Hepatology, Coma Level Classification, 12th Inuyama Symposium, 1981).[18]

DIAGNOSTIC AND TREATMENT GUIDELINES FOR EHO

Disease concept and symptoms

EHO is a syndrome in which obstruction of the extrahepatic portal vein, including the porta hepatis, leads to portal hypertension. The pathology can be classified as primary or secondary. In primary cases, it is impossible to open the obstructed portal vein radically, and the most important prognostic factor is variceal gastrointestinal bleeding. The symptoms include esophageal and gastric varices, ectopic varices, portal hypertensive gastroenteropathy, ascites, hepatic encephalopathy, bleeding tendencies, splenomegaly, anemia, and liver dysfunction. Particular attention should be paid to the duodenal bulb, where varices may form and cause intractable bleeding.[21] This guideline focuses on primary EHO and excludes secondary EHO.

CQ 5. What symptoms require treatment?

Statement: Esophageal and gastric varices, ectopic varices, portal hypertensive gastroenteropathy and biliary disease, splenomegaly, hypersplenism, and abnormal liver function represent symptoms and those need treatment. This CQ corresponds to EHO CQ E-1 in the Japanese version.

Recommendation grade: Weak recommendation (100% consensus rate).

Level of evidence: D (Low).

Etiology/pathophysiology

Although the primary etiology remains unclear, abnormalities in angiogenesis, blood coagulation, and myeloproliferative neoplasms are thought to be involved. It is generally known that the *JAK2* V617F mutation is associated with myeloproliferative neoplasms, and cases with the *JAK2* mutation have been reported in EHO.[1,22,23] In addition, decreased von Willebrand factor levels, protein C deficiency, and antithrombin III deficiency have been reported as coagulation abnormalities.[24–26]

Epidemiology

In the 2015 National Epidemiological Survey, the estimated annual number of patients with EHO was 770 (95% CI 610–930), with a prevalence of 6.1 per million population. The male-to-female ratio is approximately 1.5:1, with cases involving males being slightly more common. In the 2005 National Epidemiologic Survey, the estimated number of patients treated annually was 450 (95% CI 340–560), a slight increase from 10 years earlier. However, the number of patients in the 1999 survey was 720, and did not change significantly in the past 20 years.[5] The most common age at definitive diagnosis was <10 years, accounting for approximately 50% of the cases (patients aged in their 40s and 50s also showed a bimodal distribution, with a mean age of 33.1 years). This age distribution suggests that EHO is caused by congenital or hereditary factors. The regional characteristics of EHO were slightly more common in the Hokkaido, Tohoku, and Chugoku regions. Only one case of primary EHO has been reported to develop into hepatocellular carcinoma,[27] and the risk is extremely low.

Pathological findings

Gross examination of the liver reveals portal vein trunk obstruction and cavernous transformation. The surface of the liver is smooth. Histologically, the lobular architecture of the liver is almost normally preserved, and the intrahepatic portal vein branches are patent in some cases, but narrow in others. Mild inflammatory cell infiltration and fibrosis are observed in the portal area, but there is no evidence of cirrhosis.[28–30]

Splenomegaly is often observed. Histologically, an increase in red pulp has been reported; however, no specific pathology has been identified.[31]

Hematological findings

Peripheral blood tests showed decreased levels of one or more blood cell components. Liver function test results are often mildly abnormal.

Imaging findings

Ultrasonography

The liver surface is normal, and liver atrophy is often unremarkable. The extrahepatic portal vein, including the porta hepatis, is occluded and marked hepatopetal collateral vessels (cavernous transformation) have developed.[32]

Computed tomography and magnetic resonance imaging

Contrast-enhanced computed tomography (CT) often shows decreased staining in the hilar region, and increased staining in the hepatic subcapsular region, accompanied by splenomegaly (Figure 4A–D). Contrast-enhanced CT can also capture portal cavernous changes.[33] Contrast-enhanced three-dimensional magnetic resonance imaging portography is useful in diagnosing EHO. Additionally, magnetic resonance imaging can assist in determining the distance of the obstruction and in delineating the collateral blood vessels associated with the portal system, including the superior and inferior mesenteric veins.[34]

CQ 6. Is CT useful in the diagnosis of EHO?

Statement: CT can capture cavernous transformation of the portal vein, which is a definitive diagnostic finding in EHO. This CQ corresponds to EHO CQ B-2-2 in the Japanese version.

Recommendation level: Weak recommendation (100% consensus rate).

Level of evidence: C (Low).

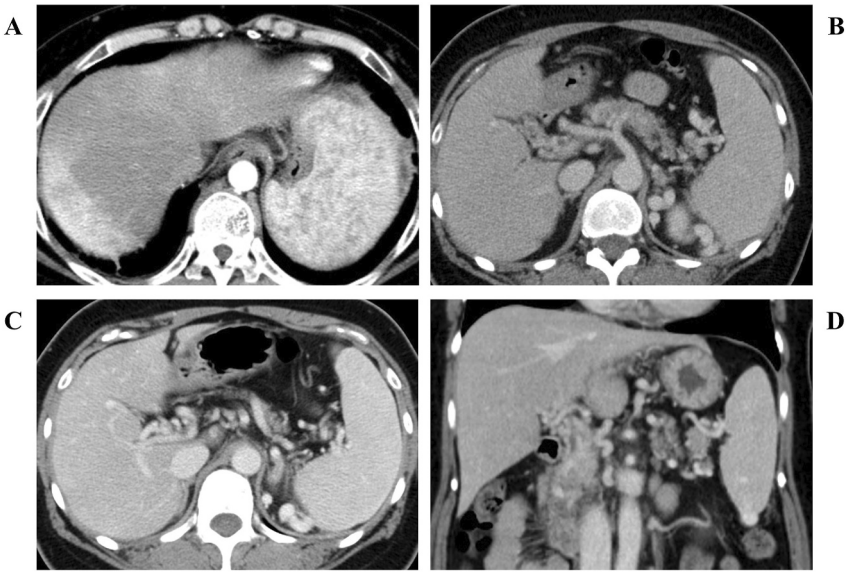


FIGURE 4 Abdominal contrast-enhanced computed tomography image. (A) In the arterial phase, there is decreased staining in the porta hepatis region and increased staining in the subhepatic capsule region. (B, C) In the portal phase, the main trunk of the portal vein disappears and is compensated by a cavernous transformation. Splenomegaly is observed, and collateral vessels have developed around the spleen. (D) Cavernous transformation can be observed in the portal phase and coronal section.

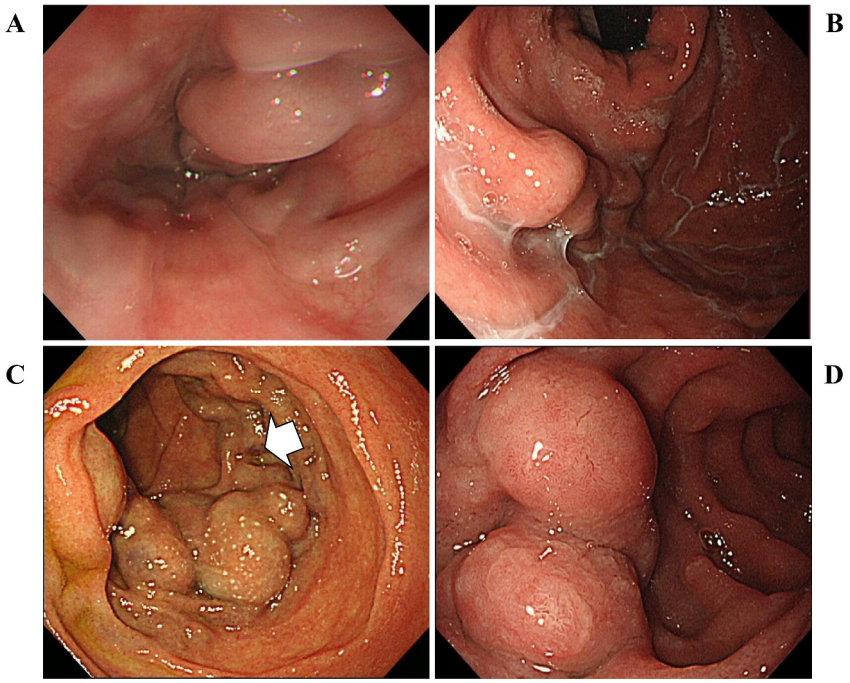


FIGURE 5 Endoscopic findings of the upper gastrointestinal tract. (A) Esophageal varices (Ls, F2, Cb, RC0). (B) Isolated gastric varices (Lg-f, F1, Cw, RC0). (C) Markedly enlarged, nodular, or tumor-shaped (F3) varices were seen in the second part of the duodenum. The red color sign is partially positive (white arrow). (D) F3 varices were seen in the second part of the duodenum. The red color sign is negative.

Endoscopy

Varices were often observed in the esophagus and stomach (Figure 5A,B). Portal hypertensive gastroenteropathy is occasionally observed. Ectopic varices are sometimes observed in the duodenum (Figure 5C,D), peribile ducts, and lower gastrointestinal tract.[35] Ectopic varices consist of portosystemic collaterals between the portal vein and the superior (or inferior) mesenteric veins that form a lumen in the gastrointestinal mucosa.

Method of diagnosis

A definitive diagnosis is obtained based on imaging findings.

Treatment

In primary EHO cases, there is no procedure for radical opening of the occluded portal vein. For portal vein thrombosis associated with cirrhosis or IPH, anticoagulation with antithrombin III preparations or danaparoid sodium is useful.[36–38] However, the efficacy for primary EHO remains unclear. Gastrointestinal variceal bleeding is the most important prognostic factor. Endoscopic hemostasis (sclerotherapy and ligation) is performed in cases of bleeding, and emergency surgery is considered when this approach fails to achieve hemostasis. Prophylactic endoscopic treatment or surgery should be considered for easily bleeding esophagogastric varices, even in cases where bleeding has not yet occurred. The treatment strategies for esophagogastric varices, ectopic varices, and splenomegaly/hypersplenism are described in Table 2.

In cases of refractory esophagogastric varices with recurrent bleeding or recurrence, which are often accompanied by splenomegaly and hypersplenism (pancytopenia), a splenectomy and direct interruption procedures, such as devascularization of the lower esophagus and upper stomach with splenectomy (Hassab's operation) or a selective shunt procedure, should be considered. Survival rates after shunt and direct interruption procedures are high, especially in children, with favorable results for the meso-Rex shunt (mesoportal bypass) creation.[39,40] As adjunctive therapies, interventional radiology treatments, such as PSE[41] and transjugular intrahepatic portosystemic shunt,[42] are also useful in controlling portal hypertension.

In Western countries, the variceal eradication rate of endoscopic injection sclerotherapy and variceal ligation for esophageal and gastric varices that develop in EHO has been reported to be 88%–100%.[39,40] The variceal recurrence rate is 8%–10% for sclerotherapy and 20%–30% for ligation.[41,42] The hemodynamics of isolated gastric varices are presumed to be more complicated in EHO due to the development of collateral blood flow; however, varices, as well as cirrhosis, can be treated using endoscopic NBCA injection and is presumed to be effective as a treatment. In a comparison of 56 cases of cirrhosis and 30 cases of EHO, EHO required the injection of a greater volume of n-butyl-2-cyanoacrylate (NBCA; 4.7 $\pm$ 3.1 vs. 3.2 $\pm$ 2.0 mL, $p = 0.014$), although rebleeding and mortality rates were not different between the two liver diseases.[43] However, because liver function is often relatively preserved in EHO, the prognosis is considered better than that for cirrhosis, even if bleeding occurs.

Injection of NBCA can be useful for ectopic variceal bleeding in EHO. In a nationwide survey of ectopic varices in Japan, 18 of 173 cases with varices originated from EHO. Endoscopic treatment was selected for duodenal varices in 31.6% of the cases, and interventional radiology was selected in 21.0%. In addition, for rectal varices, endoscopic treatment was selected in 31.9% of the cases, and interventional radiology was chosen in 5.6%, indicating that endoscopic treatment is the first treatment choice for EHO in Japan. As for the breakdown of endoscopic treatment, NBCA injection was the most common method used at 63.2%, which is a result that supports its utility.[44]

CQ 7. Is endoscopic treatment of esophageal and gastric varices in EHO effective?

Statement: Control of bleeding from esophageal and gastric varices is critical, and endoscopic injection sclerotherapy or variceal ligation is effective. This CQ corresponds to EHO CQ F-3 in the Japanese version.

Recommendation level: Weak recommendation (100% consensus rate).

Level of evidence: A (High).

CQ 8. Is endoscopic NBCA injection effective for gastric variceal bleeding in patients with EHO?

Statement: Although there are few reports of NBCA injection in EHO, this treatment is useful for gastric variceal bleeding, as in cases of cirrhosis. This CQ corresponds to EHO CQ F-5 in the Japanese version.

Recommendation level: 2 (100% consensus rate).

Level of evidence: D (Very low).

CQ 9. Is endoscopic NBCA injection useful for ectopic variceal bleeding in EHO?

Statement: As with gastric variceal bleeding, NBCA injection is useful for ectopic variceal bleeding. This CQ corresponds to EHO CQ F-7 in the Japanese version.

Recommendation level: Weak recommendation (100% consensus rate).

Level of evidence: D (Very low).

Severity classifications

Although there is no evidence of factors that define severity, esophageal and gastric varices, and ectopic varices requiring treatment are associated with severity, and as such, the severity classification is similar to that for IPH (Table 3). In children, growth disturbances may affect the determination of severity (Table 4).

TABLE 4 Pediatric severity classification of extrahepatic portal obstruction.

Factors/severity	I	II	III	IV	V
Growth retardation	–	+	+ +	+ +	+ + +

Note: The following factors may be added to the determination of disease severity in pediatric patients: growth retardation. (+): Height SD score is < −1.5 SD, > −2.0 SD; (++): height SD score is < −2 SD, > −2.5 SD; (+++): height SD score is < −2.5 SD.

Prognosis

The prognosis of EHO is relatively favorable, with reported 3- to 7-year survival rates of 90%–98% and 10-year survival rates of 69%–86%. EHO patients with EGV show favorable prognoses comparable to those without, as long as the primary or secondary prophylaxis for EGV is appropriately performed.[45]

DIAGNOSTIC AND TREATMENT GUIDELINES FOR BCS

Disease concept and symptoms

BCS is a condition in which the obstruction or stenosis of the main hepatic veins or subhepatic vena cava leads to portal hypertension. In Japan, these two syndromes are often combined. Depending on the severity of the disease, symptoms include bleeding esophageal and gastric varices, ectopic varices, portal hypertensive gastroenteropathy, ascites, hepatic encephalopathy, bleeding tendency, splenomegaly, anemia, liver dysfunction, leg edema, varicose veins of the lower extremities, and ascending subcutaneous venous distention in the thoracoabdominal wall.[1,46,47]

BCS can be divided into acute and chronic forms according to the mode of onset. The acute type generally has a poor prognosis, and presents with abdominal pain, vomiting, rapid hepatomegaly, and ascites, with a fatal outcome of liver failure within 1–4 weeks[48]; however, this type is extremely rare in Japan. In contrast, the chronic type, which accounts for 80% of the cases, often develops asymptomatically, and gradually presents with edema of the lower extremities, ascites, subcutaneous venous distention of the abdominal wall, and esophageal and gastric varices.

Etiology/pathophysiology

The etiology of this syndrome is unclear. Membranous obstruction of the subhepatic vena cava is common in Japan. Cases of membranous obstruction in the inferior vena cava, localized stenosis, or obstruction of the origin of the hepatic veins are more common in Asia and Africa, and less common in Europe and North America. The pathogenesis of this disease is hypothesized to be based on an abnormality of the ductus arteriosus of Arantius, a congenital anomaly of angiogenesis. Recently, the acquired thrombosis theory has been proposed, as the onset of the syndrome is more common in middle-aged and older patients. Moreover, a thrombus or its organizing mechanism can induce membranous structures of the inferior vena cava and localized stenosis (and obstruction) of the origin of the hepatic veins. In contrast, in Western countries, many patients with hepatic vein occlusion have underlying diseases, including hematologic diseases (e.g., polycythemia vera, paroxysmal nocturnal hemoglobinuria, myelofibrosis), oral contraceptive use, pregnancy and delivery, intra-abdominal infection, vasculitis (Behçet's disease, systemic lupus erythematosus), abnormal blood coagulation (antithrombin III deficiency, protein C deficiency), and others.[49–51]

Most cases have a chronic course (most common in Asia) with an unknown onset time, leading to congestive cirrhosis. However, acute BCS (most common in Western countries) is also observed, with symptoms due to acute obstruction or stenosis. In Asia, obstruction of the inferior vena cava is more common, whereas obstruction of the hepatic veins is more common in Western countries. There are two primary classifications: primary and secondary. The etiology of primary BCS remains unknown; however, thrombosis, abnormal angiogenesis, abnormal blood coagulation, and myeloproliferative neoplasms have been implicated. Secondary BCS is sometimes caused by liver tumors.[52]

Epidemiology

In the 2015 National Epidemiologic Survey, the estimated annual number of patients treated was 410 (95% CI 300–530), with a prevalence of 3.2 per million population. The male-to-female ratio was approximately 1:0.67, with a higher frequency in males. According to the 2005 National Epidemiologic Survey, the estimated annual number of patients with BCS was 270 (95% CI 190–360) compared with 280 (95% CI 200–360) in the 1999 survey, indicating an increase in the past 10 years.[5] The average age at the time of the confirmed diagnosis was 40.5 years. Regional characteristics showed that the disease was more common in the Tohoku, Kinki, and Sanyo regions.

Pathological findings

Gross image of the liver: Congestive hepatomegaly is observed in the acute stage, and hepatic fibrosis is associated with chronic congestion with further progression to congestive cirrhosis.[53]

Liver histology: In acute congestion, expansion of the sinusoids in the central zone of the hepatic lobule is observed, and necrosis occurs in the central zone if congestion is severe. Chronic congestive changes are visible if congestion persists, including reversed hepatic lobulation, due to fibrous connections between the centrilobular zones. As fibrosis progresses, bridging fibrosis becomes evident, mainly connecting the centrilobular zone and the portal area, leading to septal formation in congestive cirrhosis.[54]

CQ 10. Is liver biopsy useful for the diagnosis of BCS?

Statement: The basic histopathological finding in the liver associated with BCS is congestion, but no specific findings have been identified. However, liver biopsy can be used to evaluate the degree of liver congestion and the progression of liver fibrosis. This CQ corresponds to BCS CQ A-1 in the Japanese version.

Recommendation level: Weak (100% consensus rate).

Level of evidence: C (Low).

Hematological findings

Peripheral blood tests reveal decreased levels of one or more blood cell components. Liver function tests show varying degrees of impairment as the disease progresses from normal to severely abnormal.

Imaging findings

Ultrasonography and CT scan

Obstruction or stenosis of the main hepatic vein trunk or the subhepatic vena cava is observed (Figure 6).[55] Ultrasonography sometimes shows regurgitation or turbulent flow in the main hepatic vein trunk or subhepatic vena cava, and the hepatic vein blood flow waveform occasionally becomes flattened or is absent.[56,57]

Splenomegaly is often observed. Congestive liver enlargement is observed and the caudate lobe is enlarged. Liver atrophy occasionally occurs when cirrhosis develops.[58–60]

CQ 11. Is CT useful in the diagnosis of BCS?

Statement: In the diagnosis of BCS, a CT scan is useful in the diagnosis of obstruction of the inferior vena cava and hepatic veins, and in detecting parenchymal changes, including secondary intrahepatic nodular lesions. However, the detection rate for stenosis of the inferior vena cava and hepatic veins is higher with ultrasonography than with contrast-enhanced CT. Diagnosis for BCS should be performed in conjunction with contrast-enhanced CT and other imaging examination. This CQ corresponds to BCS CQ B-2-2 in the Japanese version.

Recommendation level: Weak (100% consensus rate).

Level of evidence: A (High).

Inferior vena cavography, hepatic venography, and pressure measurement

Obstruction or stenosis of the main hepatic vein trunk or the subhepatic vena cava was observed (Figure 7).[61] Various forms of subhepatic vena cava obstruction can be observed, ranging from membranous to extensive. In addition, collateral blood vessels, such as the ascending lumbar vein, azygos veins, and hemiazygos veins, are often contrasted simultaneously. There is a marked anastomosis between the branches of the hepatic veins. The subhepatic vena cava pressure is elevated, as are the hepatic venous and wedged hepatic venous pressures.[62]

Sugiura et al. classified this syndrome into four types (Figure 8).[63]

Type I is membranous obstruction of the inferior vena cava of the liver just below the diaphragm with partial patency of the hepatic vein (Ia) and total obstruction (Ib). Type II is complete occlusion of the inferior vena cava over half of the vertebral bodies.

Type III is membranous occlusion with stenosis of the entire length of the inferior vena cava. Type IV is obstruction of the hepatic veins. The frequencies of occurrence were 34.4% (Ia), 11.5% (Ib), 26.0% (II), 7.0% (III), and 5.1% (IV), respectively.

CQ 12. Is angiography useful in the diagnosis of BCS?

Statement: Angiography in cases of BCS is not necessarily essential for the diagnosis itself, but it can accurately identify the site of obstruction and measure hepatic venous pressure, which is useful in determining the subsequent treatment strategy. This CQ corresponds to BCS CQ B-2-4 in the Japanese version.

Recommendation level: Weak (100% consensus rate).

Level of evidence: C (Low).

Endoscopy

Upper gastrointestinal varices are often observed. Portal hypertensive gastroenteropathy and ectopic varices in the duodenum, peribile ducts, and gastrointestinal tract are also seen.

Method of diagnosis

A definitive diagnosis is obtained based on imaging findings and pathological examination findings.

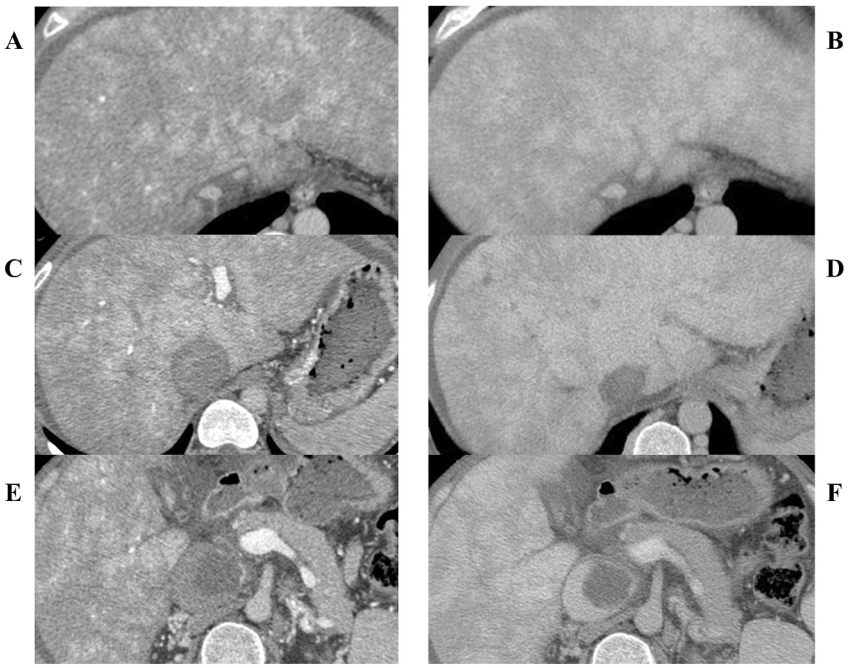


FIGURE 6 Abdominal contrast-enhanced computed tomography image. (A) Hepatic head lateral division portal phase. (B) Hepatic head lateral division equilibrium phase. (C) Hepatic hilum portal phase. (D) Hepatic hilum equilibrium phase. (E) Hepatic caudal division portal phase. (F) Hepatic caudal equilibrium phase. Partial thrombo-occlusion of the inferior vena cava is observed at the hepatic level. (A, B) The three main trunks and branches of the hepatic veins are occluded and are not contrasted. (C, D) In porta hepatis level slices, thrombo-occlusion is more advanced, and most of the lumen of the inferior vena cava is thrombosed. (E, F) Furthermore, the inferior vena cava is markedly dilated caudally, with 60% of its lumen thrombosed. The intrahepatic space is coarse and cirrhotic, and ascites is observed on the hepatic surface.

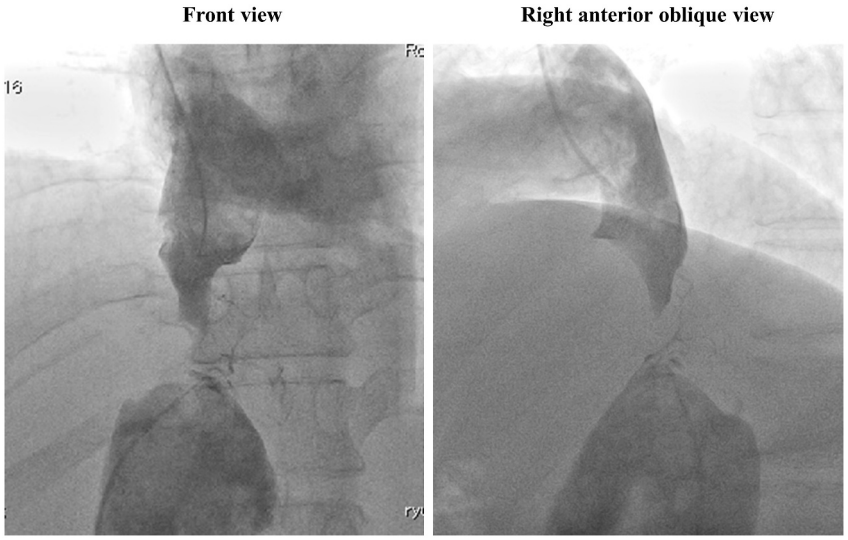


FIGURE 7 Inferior vena cavography image. A catheter was inserted through the right internal jugular and femoral veins. A portion of the inferior vena cava of the liver is completely thrombosed, and blood flow is disrupted.

Treatment

For obstruction or stenosis of the main hepatic veins or subhepatic vena cava, catheterization, dilation, stenting,[64,65] direct release surgery,[66,67] or shunt surgery in the vena cava are selected as treatment options, depending on the clinical symptoms and pathophysiology of the obstruction or stenosis.[68,69] In acute cases, when the thrombus obstructs the peripheral hepatic veins, hepatic

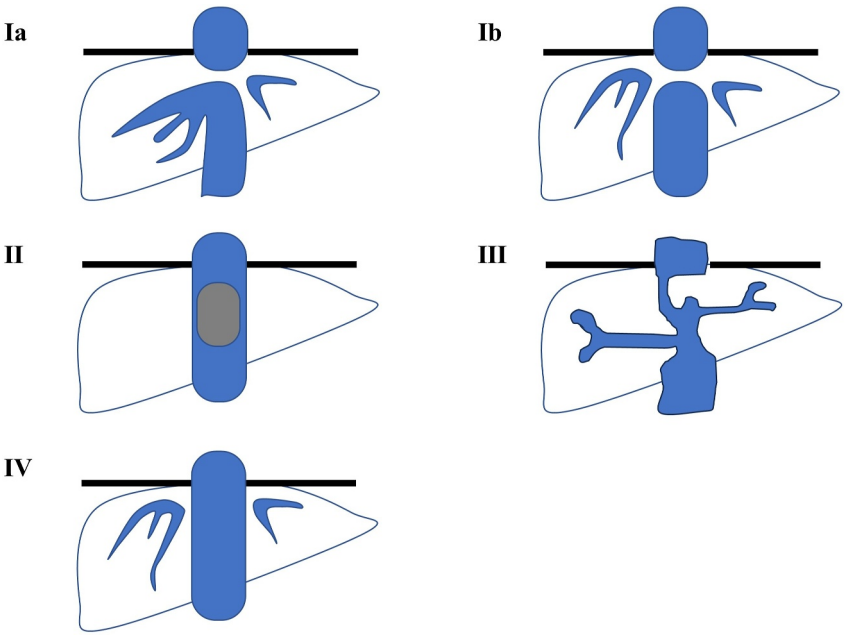


FIGURE 8 Pathological classification of Budd–Chiari syndrome by Sugiura et al.[63] Type I: Membranous obstruction of the inferior vena cava of the liver just below the diaphragm with partial patency of the hepatic vein (Ia) and total obstruction (Ib). Type II: Complete occlusion of the inferior vena cava over half of the vertebral bodies. Type III: Membranous occlusion with stenosis of the entire length of the inferior vena cava. Type IV: Obstruction of the hepatic veins.

dissection, and anastomosis between the transected plane and right atrium are options.[70,71] Liver transplantation is considered in patients with liver failure.[72]

CQ 13. Is liver transplantation effective in the case of BCS?

Statement: Liver transplantation from both deceased and living donors has been associated with favorable results in cases of BCS. This CQ corresponds to BCS CQ D-3 in the Japanese version.

Recommendation level: Weak (100% consensus rate).

Level of evidence: C (Low).

CQ 14. Is subhepatic inferior vena cava-right atrium shunt surgery indicated for inferior vena cava obstruction in cases of chronic BCS?

Statement: Among inferior vena cava obstructions in BCS, this procedure is indicated in cases of upper hepatic inferior vena cava obstruction. It is indicated only when the right atrium–inferior vena cava pressure gradient is severe (usually >12 mmHg) and there is hepatic venous outflow obstruction or symptoms of lower body congestion. This CQ corresponds to BCS CQ D-4 in the Japanese version.

Recommendation level: Weak (100% consensus rate).

Level of evidence: D (Very low).

The treatment strategies for esophagogastric varices, ectopic varices, and splenomegaly/hypersplenism are described in Table 2.

Severity classifications

Please see Table 3 for severity classifications.

Prognosis

A chronic course can lead to congestive cirrhosis.[46] The disease may also be complicated by hepatocellular carcinoma in advanced stages.[73]

CQ 15. What is the survival prognosis of BCS?

Statement: The survival prognosis of this disease has improved with recent advances in treatment techniques, with a 1-year survival rate of 90%, a 5-year survival rate of 83%, and a 10-year survival rate of 72% when limited to surveillance conducted since 2006. Patients with portal vein thrombi or thrombi in the splenic or superior mesenteric vein tend to have lower survival rates. This CQ corresponds to BCS CQ C-3 in the Japanese version.

Recommendation level: Weak (100% consensus rate).

Level of evidence: A (High).

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

ETHICS STATEMENT

Not applicable.

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