

## **Diagnosis of Hepatic Vena Cava Syndrome by Ultrasonography and Color Doppler Based on New Concept of its Pathogenesis**

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### **Abstract**

Hepatic vena cava syndrome (HVCS) is a bacterial infection induced disease of inferior vena cava (IVC) prevalent in regions of the world with poor hygienic living condition. The initial lesion that often develops early in childhood is a localized thrombophlebitis at the site where hepatic vein opens. The lesion converts on resolution into stenosis or complete obstruction followed by development of cavo-caval collaterals. These changes persist throughout the life. During subsequent bacteremia infection deposition of thrombus occur at the abnormal segment of the vein resulting in acute exacerbations (AE). The thrombus so formed may extend into hepatic veins resulting in thrombophlebitis of the intra-hepatic vein and development of ascites from hepatic venous outflow obstruction (HVOO). HVOO or intra-hepatic vein thrombophlebitis induced ischemic liver damage results in development of cirrhosis.

HVCS is characterized by long asymptomatic period and recurrent mild jaundice and/or ALT/AST elevation or ascites and high incidence of hypersplenism, liver cirrhosis (LC) and hepatocellular carcinoma (HCC). Ultrasonography and color Doppler (US/CD) examination of IVC and liver recognizes the different phases of the disease and distinctive features in HVCS induced LC making it the first choice of investigation for its diagnosis.

HVCS was recognized as a common co-morbid condition of patients with chronic hepatitis B in Nepal. As HVCS occurs in geographic areas of the world with intermediate to high prevalence of chronic hepatitis B (CHB) for its proper management in developing countries identification of co-existing HVCS and the exact cause of ALT/AST elevation and development of cirrhosis need to be determined.

**Keywords:** *Budd-Chiari Syndrome; Membranous Obstruction of Inferior Vena Cava; Hypersplenism; Ascites; Hepatic Venous Outflow Obstruction; Liver Cirrhosis; Hepatocellular Carcinoma*

### **Introduction**

Hepatic vena cava syndrome (HVCS) is a chronic disease of the hepatic portion of the inferior vena cava (IVC) previously described as membranous obstruction of inferior vena cava (MOVC) or Budd-Chiari syndrome (BCS) [1-5]. It is clinically characterized by decades of uneventful course at one end to rapidly fatal fulminant course with ascites and jaundice at the other end [5]. The disease is associated with high incidences of liver cirrhosis (LC) and moderate to high incidence of hepatocellular carcinoma (HCC) [1,2,5,6]. The disease had occurred in the West [7-14] and in Japan [15-20], but is now confined to Afro-Asian countries [1-4,21-32].

In the past HVCS was considered a congenital vascular malformation and diagnosed late at autopsy [2,7-10] or in symptomatic patient with complete IVC obstruction [1-4,17,20,22,28]. Liver biopsy and cavogram were considered gold standard diagnostic procedures. Occurrence of centrilobular congestion or ischemic necrosis or its sequel venocentric cirrhosis in liver biopsy indicated presence of HVCS [1,3,5,32]. Majority of the patients in early stage however have no liver damage. And biopsy findings in the disease varied from normal or minimal changes like sinusoidal dilatation, mild central vein fibrosis; mild periportal fibrosis with or without inflammatory infiltration, endophlebitis or thrombosis of sublobular vein to venocentric and veno-portal types of cirrhosis [5,10,18,24,32-34]. Some changes like

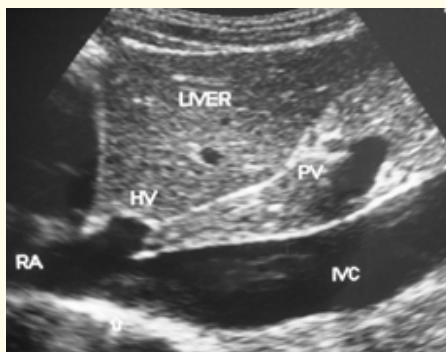
portal inflammatory changes or fibrosis may be wrongly interpreted as chronic hepatitis and advanced cirrhosis from it may be histologically indistinguishable from that due to other causes. Further, histology is not helpful to predict the duration of the disease as mixed features of congestion and cirrhosis occur both in 'acute' and chronic stages [5,29,33], and the lesions of different ages are present at the time of death' [33,34]. The acute changes and its sequel veno-centric cirrhosis occur in other diseases that causes hepatic venous outflow obstruction (HVVO) like sinusoidal obstruction syndrome (SOS) and Budd Chiari syndrome (BCS). Liver biopsy thus is not the choice of first investigation in HVCS. Cavogram is helpful in diagnosis and especially invaluable for the study of collateral anastomosis. The procedure however will miss the diagnosis in large number of patient with minimal to mild stenosis of the IVC. In the West long segment narrowing of IVC is due to compression by large caudate lobe in patients with BCS [35]. Long segment stenosis of the hepatic portion of the IVC, the commonest type of lesion seen in HVCS may thus be misinterpreted as caused by caudate lobe enlargement [36]. In patients with advanced disease the oblitative lesion may fail to outline as the contrast medium rapidly runs off into large collaterals [2]. Both these procedures are invasive and require hospitalization and need expertise for interpretation and are costly and not without risk and as such are unlikely to be used as a routine diagnostic tool.

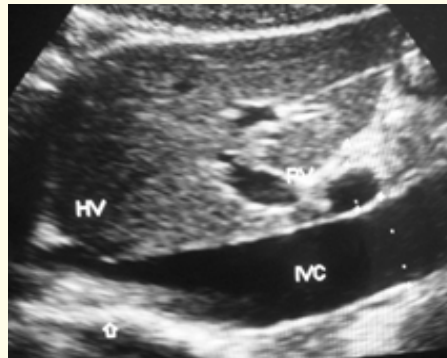
HVCS is often seen children [13,14,31,32,47]. It is prevalent in areas with poor standard of hygiene [30,37,38]. It is now known to be related to bacterial infection [39], a new concept of its pathogenesis described [39-41]. Ultrasonography had been used in the diagnosis of HVCS [42]. This paper describes the use of ultrasonography and color Doppler (US/CD) based on the understanding of its pathogenesis in the diagnosis of HVCS.

**Ultrasonography and Color Doppler diagnosis in of HVCS**

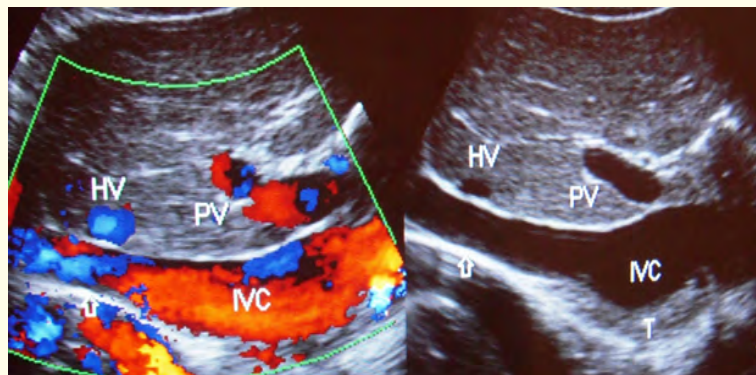
**Acute HVCS:** The initial lesion in HVCS is a localized thrombophlebitis that typically occurs on posterior wall of the IVC at the site where hepatic veins opens. Acute lesion was identified in cavogram as a large oval filling defect, and early development of collateral vessels in IVC [40]. In US/CD it is recognized as a localized thrombus on thickened posterior wall (Figure 1a, 1b). Routine use of this procedure in patients with bacterial infection is likely to widen the diagnostic net.

**Chronic HVCS:** Spontaneous resolution of the acute lesion results in development of localized stenosis or rarely a complete obstruction (Figure 1c, 1d). The stenosis may be minimal with just thickened posterior wall or mild to moderate. These developments goes unnoticed as it causes no significant change in the circulation except for dilatation of the vein for a short distance distal to the lesion and development of cavo-caval collateral anastomosis. Several pathways of collateral anastomosis develop [11]. Superficial collaterals are seen as dilated superficial veins in abdomen and chest wall or in lumbar region in the back with upward flow. Deep collaterals are more constant and include ascending lumbar veins, azygous vein and hemiazygous veins. With the circulatory balance restored duration of the life is unaffected by the severity or extent of caval obstruction [11,41]. About 25% of the patients with HVCS have splenomegaly with evidence of hypersplenism with platelet count < 150,000/cu mm and or WBV count < 3500 per cu mm with or without anemia.

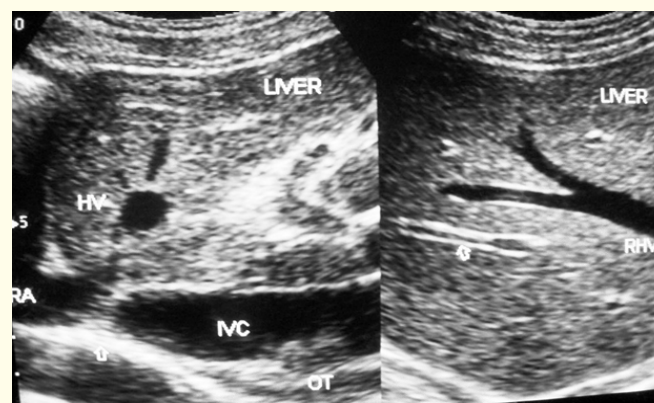




**Figure 1a and 1b:** Acute thrombophlebitis: ultrasonography of a patient with gut infection and *E. coli* bacteremia showing development of a localized thrombophlebitis-thrombus on a thickened posterior wall of the IVC opposite the site of hepatic veins opening.



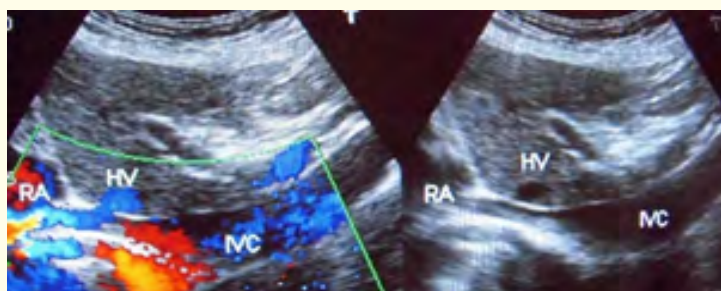
**Figure 1c:** Stenosis of IVC-sequel of acute thrombophlebitis: ultrasonography and color Doppler study showing stenosis of a long segment of IVC at cavo-atrial junction-a sequel of initial acute lesion. Note the distal dilated segment of IVC with organized thrombus on posterior wall formed during acute exacerbation.



**Figure 1d:** Membranous obstruction of IVC-sequel of acute thrombophlebitis: ultrasonography showing a thick membrane formed at the stenosed segment of the IVC at cavo-atrial junction after resolution of the initial acute lesion. Also note the presence of old organized thrombi of different ages along posterior wall of distal dilated segment, one thrombosed medium sized intra-hepatic vein and dilated main hepatic veins with membrane in middle hepatic vein with irregular caliber. Liver parenchyma shows increase echo-texture compatible with development of fibrosis.

**Acute Exacerbations:** The abnormal segment of the vein becomes vulnerable to subsequent bacterial infections with deposition of fresh thrombus resulting in acute exacerbations (AE). AE precipitated by clinical or subclinical bacterial infection manifest clinically as recurrent mild jaundice or minimal to mild elevation of ALT/AST often associated with fever, neutrophil leukocytosis or L-shift and high level of C-reactive protein (CRP) or bacteremia. Patients with leucopenia due to hypersplenism develop frequent AEs and self-limiting esophageal variceal bleeding from transient portal hypertension as indicated by presence of low-grade varix that disappear later.

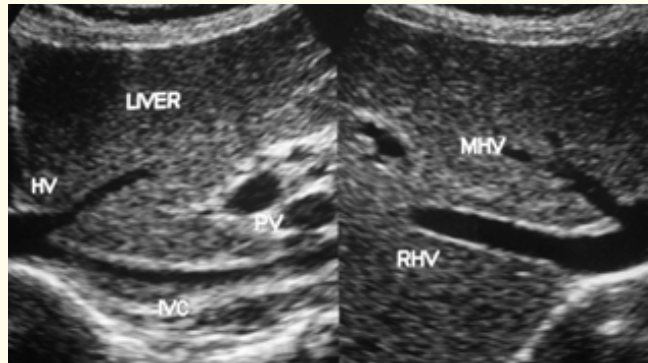
Presence of old organized thrombi of different ages in IVC, probably deposited at different periods was reported in autopsy studies of the patients in the past [8,15-18,33]. Histology of the thrombus showed various degree of organization and development of capillaries or calcification [34]. Changes in IVC caused by AE or recurrent AEs whether clinically evident or silent are recognizable in US/CD examination. During AE thrombus is deposited at the site of initial lesion (Figure 2a) or along posterior wall of the distal dilated segment of the vein (Figure 2b). Gallbladder wall appear thick and edematous. Occurrence of recurrent AEs is recognized by presence of thrombi of different ages at the site of the lesion and/or along posterior wall of the distal dilated segment of the IVC (Figure 2c-2f). Thrombi formed during recurrent AEs may completely occlude the lumen of the IVC (Figure 2d). These in course of time get organized as layers of linear thrombi along the posterior wall with development of capillaries in it (Figure 2f). This process distorts the shape of the IVC, which explains for the different patterns of IVC reported by earlier workers in cavogram [20,28]. Organization of the thrombi deposited at the original site of lesion eventually converts it into a shrunken narrowed fibrous cord like structure of variable length (Figure 2g) as was reported by Osler in an autopsy study [8].



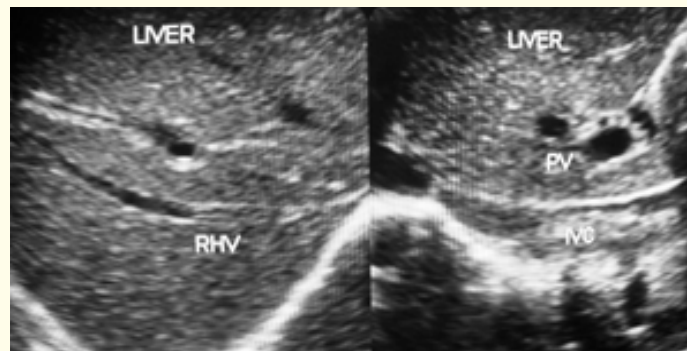
**Figure 2a:** Acute exacerbation with thrombus deposited at the site of lesion: ultrasonography and color Doppler of IVC showing a long segment stenosis with deposition of thrombus during AE. Note the distal dilated segment.



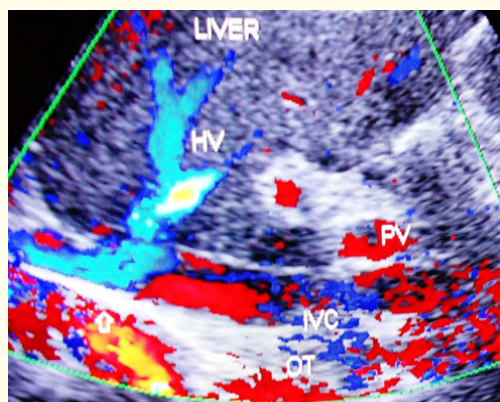
**Figure 2b:** Acute exacerbation: ultrasonography showing a large organized thrombus formed during AE along the posterior wall just distal to localized stenosis.



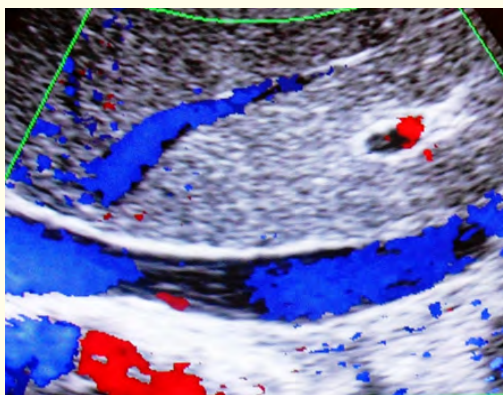
**Figure 2c:** Recurrent AE: thrombi of different ages in the IVC along the posterior wall almost filling the lumen of the vein indicative of occurrence or recurrent AE. Note the thickened wall of the IVC and thick echoic thick all of right hepatic vein, and liver parenchyma with diffuse fibrosis.



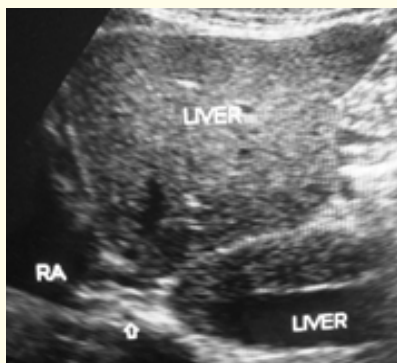
**Figure 2d:** Recurrent AE: two large thrombi of different ages filling the lumen of the IVC indicative of recurrent AE. Note the thrombus entering right hepatic vein, thrombosed branch of portal vein and liver showing features of fibrosis.



**Figure 2e:** Recurrent AE: color Doppler showing stenosis of the IVC at cavo-atrial junction and large irregular organized thrombus extending from the lesion to distal dilated segment of the IVC along its posterior wall. Note increased echogenicity around the portal vein and liver with features of fibrosis.



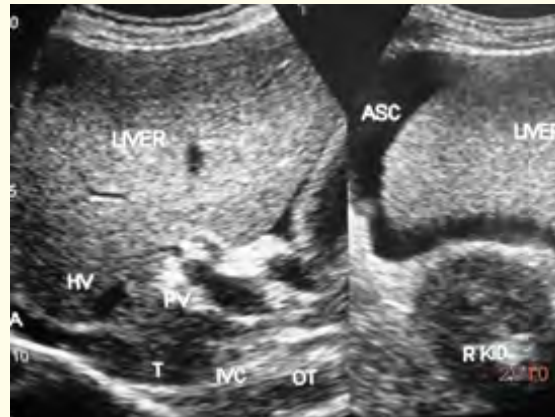
**Figure 2f:** Sequel of recurrent AE: color Doppler showing stenosis of IVC at cavo-atrial junction and the posterior wall of the distal dilated segment of IVC filled with layers of organized thrombi showing capillarization. Note the very thick wall of the IVC, a long segment of middle hepatic vein stenosed and liver showing of features of uniform fibrosis.



**Figure 2g:** Sequel of recurrent AE: long segment complete obstruction of IVC at cavo-atrial junction by organization of thrombi formed at the site of lesion during recurrent AE.

**Ascites from Severe AE:** Thrombus formed at the hepatic vein outlets during acute stage or AE that causes hepatic venous outflow obstruction (HVVO) results in sudden development of high protein content ascites. It is associated with pleural effusion in about 15% of the patient [43]. Ascites in HVCS develops at any age and at any stage of the disease- acute phase or even after development of LC or HCC and may be recurrent. It is more likely in persons with poor nutrition during puerperal sepsis [11,27], chronic diarrhea or periods of alcohol abuse or precipitated by surgery [44].

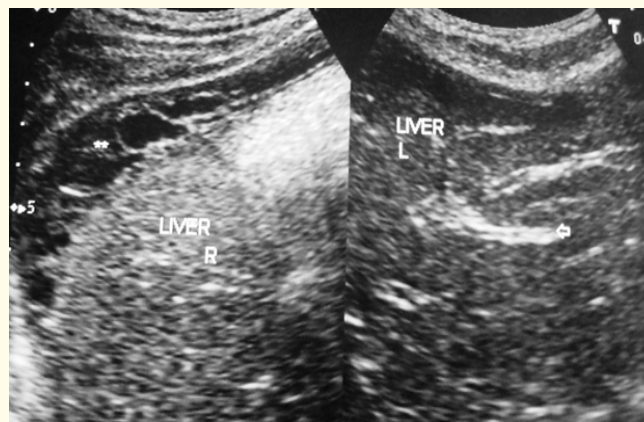
HVCS induced ascites is associated with bacterial peritonitis [45]. US/CD examination recognizes severe AE as presence of ascites, hepatomegaly with obstruction to blood flow in hepatic veins and recent and old organized thrombi in IVC at hepatic vein outlet (Figure 3a-3d). Presence of acute bacterial peritonitis is indicated by free-floating particles in the ascitic fluid that settles on standing (Figure 3b) and chronic peritonitis by thickened peritoneal wall and/or multiple adhesions (Figure 4d). Investigation at early stage of the disease detects bacteremia, neutrophil leukocytosis and marked elevation of CRP.



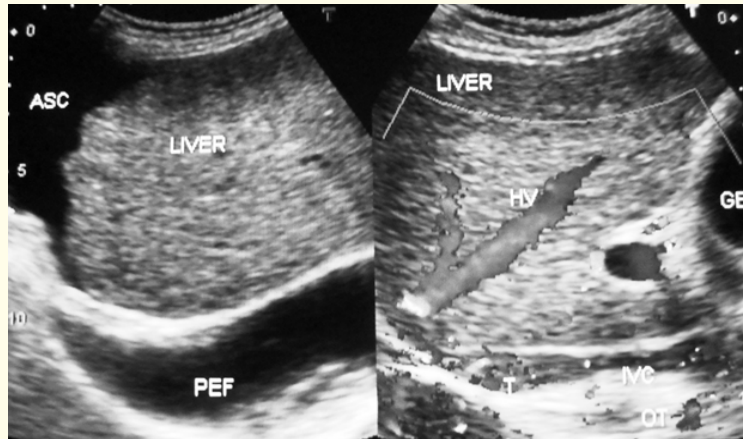
**Figure 3a:** Ascites from severe AE: US show hepatomegaly with uniform increased echo-texture and ascites. IVC shows stenosis at cavo-atrial junction and large recent and old thrombus.



**Figure 3b:** Ascites with evidence of acute bacterial peritonitis: free-floating particles in the peritoneal cavity settled down on standing.



**Figure 3c:** Ascites with evidence of chronic bacterial peritonitis: Ascites with thick peritoneal wall and multiple adhesions. Liver shows features of LC with thrombosed medium-sized intra-hepatic veins.



**Figure 3d:** Ascites with pleural effusion: ultrasonography of a patient with HVCS induced LC who developed ascites and pleural effusion from AE.

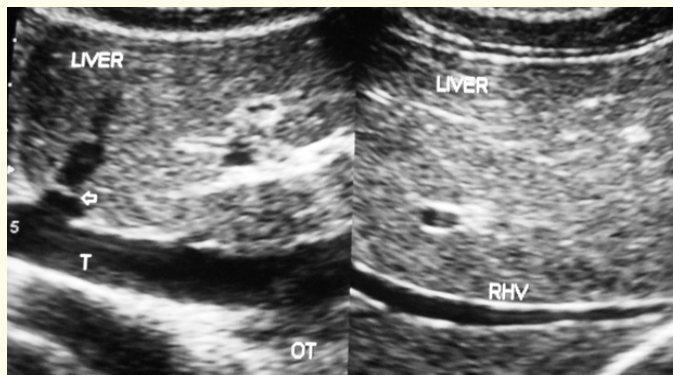
In developing countries ascites in young subject is often considered due to tuberculosis and treated so without much work up. Misdiagnosis can be prevented by routine US/CD examination of IVC and liver in patient with ascites followed by laboratory investigations that include total and differential WBC count of blood, CRP, liver function tests and assay of ascitic fluid for protein, albumin, total and differential WBC count and culture of blood and ascitic fluid for aerobic organisms by bed-side inoculation in blood culture bottle.

**Thrombosis of Intra-hepatic Veins from AE:** Because of the unique site of the initial lesion, the thrombus formed in IVC during AEs extends into adjoining hepatic veins. Occurrence of thrombophlebitis of medium-sized intra-hepatic veins with ischemic necrosis of the hepatocytes had been documented in autopsy and liver biopsy studies [10,46]. US/CD examination of liver recognizes intra-hepatic thrombosis and its sequel (Figure 4a-4e). Thrombus that extends into right hepatic vein causes thrombosis of its tributaries, thickening of its wall and which ultimately leads to its conversion into a cord like structure. Other sequel of intra-hepatic vein thrombosis include segmental stenosis of middle hepatic vein and other medium-sized intra-hepatic veins, membrane inside middle hepatic vein (Figure 4b) and at the outlet of middle and left HVs (Figure 4c) and calcification on the vein wall (Figure 4d). Segmental obliteration of intra-hepatic vein is followed by development of collaterals within (Figure 4e) and around the liver. Children with HVCS and bacteremia are likely to develop diffuse involvement of intra-hepatic veins (Figure 4a) [47].

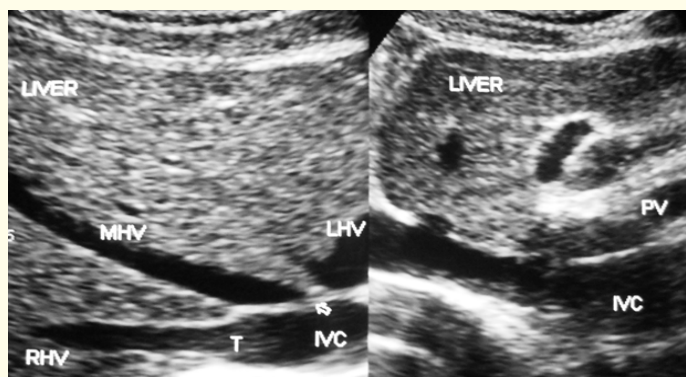


**Figure 4a:** AE with involvement of intra-hepatic veins: ultrasonography of a young boy with involvement of intra-hepatic veins during AEs. Note thick echoic wall of right hepatic vein, diffuse echoic medium-sized intra-hepatic veins.





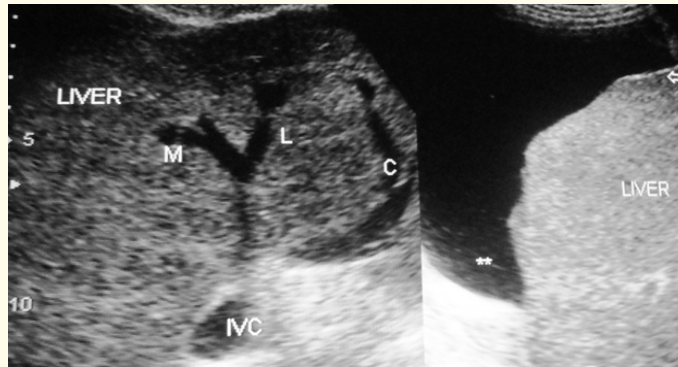
**Figure 4b:** Membranes inside MHV: Note thick echoic wall of RHV and portal vein branches. IVC shows stenosis with fresh thrombus and old organized thrombus on posterior wall and increase echo-texture of liver.



**Figure 4c:** Thick membrane at the common outlet of M & L HVs and thrombus at RHV outlet: IVC shows stenosis at cavo-atrial junction. Note the increase coarse echo-texture of the liver.



**Figure 4d:** Calcified foci in the liver: Calcified foci seen in the wall of MHV wall. It also has a thick membrane at its outlet. IVC shows mild stenosis with layers of old organized thrombi along its posterior wall.

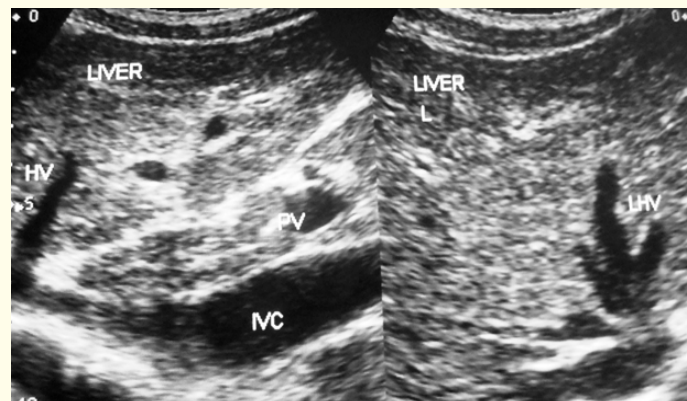


**Figure 4e:** Collateral in the liver: of a HVCS induced LC patients due to segmental obliteration of M & HV. Also note the development of ascites with bacterial peritonitis during AE.

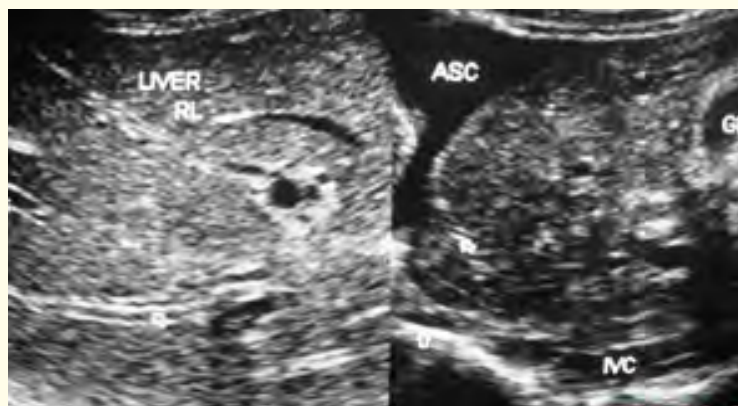
**Cirrhosis in HVCS:** HVOO induced ascites is a pre-cirrhotic condition. It is associated with venocentric ischemic necrosis of hepatocytes followed by development of fibrosis and regenerative nodules around periportal area within a few weeks and veno-centric liver cirrhosis within a few months [6,46-49]. Similarly thrombosis of intra-hepatic veins that develop during AE causes ischemic necrosis of hepatocytes drained by the vessels followed by of veno-portal type of cirrhosis [46-49].

HVCS induced LC is characterized by some distinctive clinical and US/CD features [50]. In HVCS cirrhosis develops equally in children and adult of either sex. Compared to alcohol or chronic hepatitis B and C virus infections cirrhosis develops rapidly even in early stage of the disease. Patients with HVCS induced cirrhosis rarely have vascular spiders, palmer erythema, or coagulopathy, but symptoms of recurrent AE like recurrent ascites or pleural effusion (Figure 3d, 5b) or self-limiting esophageal variceal bleeding from transient portal hypertension are common and these responds to medical treatment. Ascites occurring in HVCS induced LC is not indication of progressive liver failure and indication for liver transplantation as in alcoholic cirrhosis. Question arise can we identify HVCS induced cirrhosis?

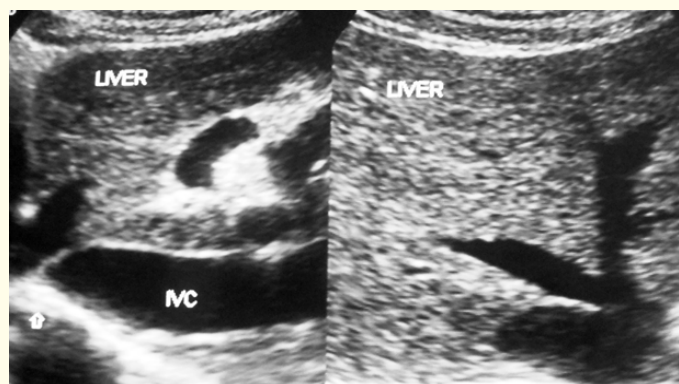
HVCS induced LC is characterized by some distinctive US/CD features. Whereas in LC due to other causes hepatic veins are attenuated in HVCS it is prominent and may even be dilated (Figure 5a, 5c). Presence of features like thrombosed right hepatic vein, echoic intra-hepatic veins (Figure 5b), membrane inside hepatic veins (Figure) or at common orifices of middle and left hepatic vein, collateral in the liver or around it (Figure 4e), calcified foci or thick gallbladder indicate to HVCS induce LC.



**Figure 5a:** HVCS induced LC with dilated HVs: IVC shows stenosis with thrombosis. Note the dilated distal segment with thick organized thrombus on posterior wall.



**Figure 5b:** HVCS induced LC with diffuse echoic intra-hepatic veins and ascites and thick GB wall and IVC filled with organized thrombus—due to recurrent AEs.



**Figure 5c:** LC detected in a CHB patients with inactive carrier state (HBeAg negative, anti-HBe positive and very low HBV DNA): membrane at cavo-atrial junction with thick organized thrombus on posterior wall and dilated HVs compatible with LC due to HVCS.

**HVCS as a co-morbid condition with other liver diseases in developing countries:** HVCS is a common co-morbid condition of patients with CHB related LC and HCC in Nepal [49]. It is possible such situation exists in other developing countries with intermediate or high prevalence of CHB and poor hygienic living condition. China with high prevalence of CHB also has high incidence HVCS [24,25]. The need for antiviral therapy in CHB is determined by presence of ALT elevation and HBV DNA level. HBeAg positive CHB person with very high HBV DNA level and normal ALT level has immune tolerant phase and do not require anti-viral therapy. Similarly HBeAg negative CHB with low HBV DNA with normal ALT has inactive carrier state and do not require anti-viral therapy. If these patients have persistent or intermittent ALT elevation related to CHB infection they may be in immune active phase and require anti-viral therapy. Identification of the exact cause of ALT elevation and that of LC in CHB patient with HVCS co-morbid condition is thus important in deciding the treatment. ALT elevation associated with bacterial infection, bacteremia or neutrophil leukocytosis or high level of CRP, and that returns to normal with antibiotic therapy is probably due to AE of HVCS. Similarly LC in CHB patient may be due to associated HVCS (Figure 5c) requiring different approach in management when ascites develops. It is suggested that patients with CHB and other liver diseases in developing countries should have an initial US/CD examination to identify the presence of HVCS.

## Conclusion

Hepatic vena cava syndrome is a bacterial infection induced disease of IVC characterized by long asymptomatic period and recurrent AEs with a potential to cause recurrent ischemic liver damage, ascites, hypersplenism, LC and HCC. The disease is prevalent in areas of the world with poor hygienic living condition. Its diagnosis depends on the detection of the lesion at the hepatic portion of IVC and identification of bacterial infection induced AEs. US/CD examination of IVC and liver along with the laboratory tests done at appropriate time was found helpful in its diagnosis. As it exist as co-morbid condition with other liver diseases proper management of the patient demands identification of the exact cause of ALT elevation or LC.

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