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POINT-OF-VIEW

Association of acute-on-chronic liver failure with vascular liver diseases

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Introduction

Acute-on-chronic liver failure (ACLF) is defined as acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28-day mortality [1]. Budd–Chiari syndrome and portal vein thrombosis (PVT) are two commonest vascular liver disorders but their association with ACLF has not been systematically evaluated. In patients with ACLF with acute event of venous thrombosis like PVT or hepatic vein thrombosis, there is a potential for reversibility of liver failure. We believe that all attempts need to be made towards urgent recanalization of the recently thrombosed vein(s) especially in the 'golden window' to achieve this reversibility. This article presents the personal point of view of the authors regarding the possible associations, pathological basis, clinical impact and management strategies of these disorders.

The association of PVT and ACLF

We believe, there could be three possible associations of PVT and ACLF (PVT–ACLF) (Table 1). In the type A PVT–ACLF, acute occlusive PVT precipitates ACLF in a patient with a previously diagnosed or undiagnosed chronic liver disease. In a recent case report, a 68-year-old patient with alcoholic liver cirrhosis, developed ACLF due to variceal bleed, precipitated by acute PVT and was successfully managed with TIPS [2]. Another mechanism for precipitation of ACLF could be reduction of hepatic blood flow due to acute PVT leading to ischemic liver injury. PVT, the fourth commonest potential precipitating event of ACLF in patients with hepatitis B (6.5%), was less common among those with ACLF than those without, suggesting that PVT precipitates ACLF in a small proportion of patients [3]. Another situation of PVT–ACLF would be development of ACLF in a patient with pre-existing chronic liver disease and PVT (Type B PVT–ACLF). The natural history and outcome of this entity is expected to be similar to those without PVT. A third association could be development of acute PVT, following onset of ACLF (Type C PVT–ACLF). Factors that may predispose patients with ACLF to develop vascular thrombosis are elevation of VWF antigen and activity, portal venous stasis and endotoxemia. Acute occlusive PVT in an early cirrhotic liver possibly leads to worse outcomes than those with advanced cirrhosis, due to compensatory increase in hepatic arterial flow in the latter due to sluggish or reversed PV flow [4].

Treatment of PVT–ACLF

In patients with type A PVT–ACLF, all attempts at recanalization should be made as there may be potential for reversibility. Anticoagulation is recommended in all patients with acute occlusive PVT and enoxaparin (1 mg/kg body weight twice daily) is often used initially. Those with associated small bowel ischemia need urgent intervention; surgery in presence of bowel gangrene and anticoagulation or thrombolysis in others. Our algorithm for management of PVT–ACLF is mentioned in Fig. 1. A unique situation in PVT–ACLF would be if the chronic disease is BCS and acute event is PVT. Those with previously undiagnosed or untreated BCS would benefit by urgent TIPS and thrombolysis/thrombus aspiration from portal vein. In patients with previous TIPS for BCS, thrombolysis, mechanical thrombectomy or thrombus aspiration through TIPS would be preferred.

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Table 1 Types of possible associations of vascular liver diseases and ACLF

Types of PVT–ACLF	
Type A	PVT is the acute hepatic insult for precipitating ACLF in a patient with previously known or unknown chronic liver disease
Type B	ACLF develops in patients with pre-existing PVT and previously known or unknown chronic liver disease
Type C	Acute PVT develops after development of ACLF
Types of BCS–ACLF	
Type A	New acute HV obstruction, extension of HV thrombosis or previous HV/TIPS stent block precipitates ACLF in a patient with previously diagnosed or undiagnosed BCS
Type B	Acute insult unrelated to BCS in a patient with previously diagnosed or undiagnosed chronic BCS
Type C	Acute HV thrombosis in a patient with unrelated previously diagnosed or undiagnosed chronic liver disease other than BCS

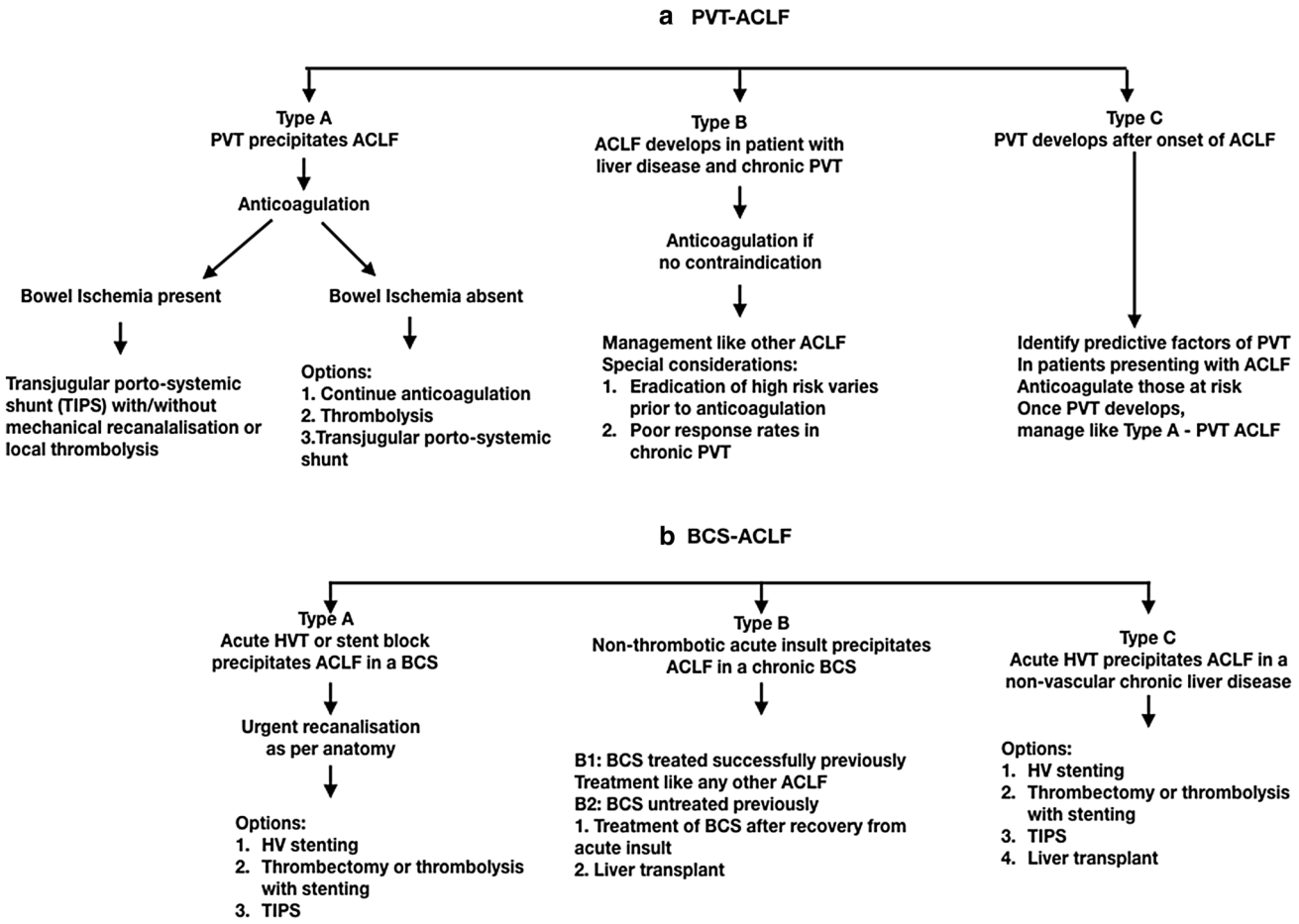

Fig. 1 Treatment algorithms for management of PVT–ACLF (**a**) and BCS–ACLF (**b**)

Radiological interventions such as local thrombolysis, mechanical recanalisation and transjugular intrahepatic portosystemic shunt (TIPS) can be attempted in patients with PVT–ACLF (Fig. 1). Thrombolytics (usually urokinase according to patient weight [< 65 kg: 80,000IE/h; > 65 kg: 100,000IE/h]) are infused into the portal vein directly via percutaneous, transhepatic or transjugular approach or indirectly by injection into the superior mesenteric artery. The best results of thrombolysis are achieved if the thrombus is less than 14 days old. Thrombolysis is done by mechanical thrombectomy (usually after impregnating the thrombus with 100,000 IE. Urokinase) or balloon angioplasty, which may be combined with local thrombolysis. Percutaneous transhepatic balloon angioplasty and/or stent placement

is an alternative. TIPS may be combined with portal vein thrombectomy for access and to ensure fast blood flow in the portal vein, thereby reducing the risk of re-thrombosis.

BCS and ACLF

The other vascular liver disease which may have acute-on-chronic presentation is BCS. The survival of patients with acute-on-chronic BCS is 55% at 10 years as compared to more than 90% with other presentations [5]. There are three possible associations of BCS and ACLF (BCS–ACLF) (Table 1). In the first, patients with previously diagnosed or undiagnosed BCS develop ACLF due to acute HV obstruction, extension of HV thrombosis, re-occlusion of a recanalised vein or occlusion of a HV/TIPS stent (Type A BCS–ACLF). In a series of 15 patients with BCS, managed with TIPS, eight with progressive liver failure had worse outcomes as compared to those with chronic BCS [6]. The entity of ACLF was not described until then but the clinical features of these patients (coagulopathy, encephalopathy, increasing jaundice and ascites) suggest presence of ACLF. Secondly, a patient with previously diagnosed or undiagnosed BCS may develop ACLF due to unrelated acute insult like hepatitis E, drug induced liver injury, etc (Type B BCS–ACLF). In a series of patients with ACLF, precipitated by acute hepatitis A and/or hepatitis E, two patients were reported to have chronic BCS as the etiology of chronic liver disease [7]. Lastly, acute HVT or IVC thrombosis may be the acute insult in patients with pre-existing chronic liver disease (Type C BCS–ACLF). In a case report from Singapore, a 64-year-old male with chronic hepatic B and regenerative nodule developed liver failure following hepatic vein thrombosis and died within 16 days [8].

Acute-on-chronic BCS is diagnosed by presence of one acute and one chronic clinical, histological or radiological feature; acute features included right upper quadrant abdominal pain, AST > 5 ULN, and liver cell loss at biopsy. Chronic features include previous hospitalization for unexplained symptoms (which regressed spontaneously and that were later related to Budd–Chiari syndrome), splenomegaly, combination of atrophy/hypertrophy of liver lobes, and centrilobular fibrosis or cirrhosis at liver biopsy if available. These criteria have limitations. Abdominal pain may have multiple etiologies and liver biopsy is difficult to perform due to ascites, coagulopathy and difficulty in cannulating the hepatic veins.

Radiology can be relied upon to distinguish acute and chronic HVT. The spectrum of changes of acute HVT includes acute thrombosis of hepatic veins, extension of previous hepatic vein thrombosis, occlusion of a large collateral or accessory hepatic vein. The changes associated with chronic HVT include atrophy/hypertrophy of liver lobes, presence of a chronic thrombus or cord-like transformation of hepatic vein and/or inferior vena cava (IVC), presence of IVC membrane or stenosis and enlarged accessory hepatic veins. Accuracy of diagnostic criteria for acute-on-chronic BCS may be improved by incorporating radiological features. The disease burden, clinical picture, prognosis and treatment strategies of BCS presenting as ACLF have not been studied and should be an area of future research.

Treatment of BCS–ACLF

There are few data on management of patients with BCS–ACLF. Our proposed treatment algorithm of HVT–ACLF is outlined in Fig. 1. Liver failure may be reversed by treating the acute event in the golden therapeutic period. Therefore, all attempts should be made to ameliorate the precipitating events as soon as possible. Urgent attempts at recanalization are recommended for acute HVT or stent block (type A BCS–ACLF). Inclusion of therapy for untreated chronic BCS would be recommended in type C BCS–ACLF.

Role of liver transplantation in management of vascular liver diseases and ACLF

The presence of extra-hepatic organ failure, a defining feature of ACLF according to the Chronic Liver Failure Consortium (CLIF-C), would indicate worse prognosis and lower threshold for liver transplant. Patients with vascular liver diseases and ACLF who have not responded or have contraindications to radiological intervention should be recommended early liver transplant [8]. Liver transplant for BCS is safe and effective, except for slightly higher risk of vascular thrombosis after transplant and technical challenges due to thrombosed IVC and occasionally, TIPS stent extending into the main portal vein, supra-hepatic IVC or right atrium. In patients with PVT, extension of thrombosis into SMV and/or bowel ischemia may pose unique challenge and may even preclude liver transplant. In general, the presence of PVT at time of liver transplant is associated with slightly worse outcomes.

Conclusions

PVT–ACLF and BCS–ACLF are rare and poorly studied entities but have significant clinical implications. In patients with ACLF, where the acute event is venous thrombosis, all attempts need to be made towards re-establishing adequate blood flow. Other patients may be managed as per standard of care for ACLF. The clinical course, treatment options and prognosis of PVT–ACLF and BCS–ACLF, need to be studied in prospective focused multi-center studies and would add value to the syndrome of ACLF.

Compliance with ethical standards

Human and animal rights This article does not contain any studies with human or animal subjects.

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