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EDITORIAL

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Identifying the four shades of acute decompensation of cirrhosis

Liver cirrhosis is traditionally classified into an asymptomatic phase, namely "compensated" cirrhosis, and a symptomatic phase, namely "decompensated" cirrhosis, characterized by the occurrence of complications of cirrhosis (ascites, variceal bleeding, and hepatic encephalopathy), which are associated with poor survival and quality of life.[1] Decompensation usually occurs suddenly leading to hospitalization (acute decompensation [AD]). Although the occurrence of AD is well known to mark the transition from compensated to decompensated cirrhosis, recent findings suggest that patients with AD are quite heterogeneous. The CANONIC study clearly identified a specific subgroup of patients with AD characterized by severe systemic inflammation, organ failures, mitochondrial dysfunction, and high short-term mortality (>15% at 28 days).[2–4] This distinct syndrome has been called acute on chronic liver failure (ACLF), involves about one-third of patients with AD[2] and occurs in about 40% of patients with cirrhosis within 10 years.[5] However, in clinical practice, patients with AD without ACLF still constitute a heterogeneous group of patients.

The PREDICT study recently described three different clinical courses of AD with different pathophysiology and prognosis: stable decompensated cirrhosis (SDC), unstable decompensated cirrhosis (UDC), and pre-ACLF.[6] Patients with SDC did not develop ACLF; they neither require readmission nor die during the 3 months after the enrollment. The clinical course of SDC is characterized by a very low 1-year mortality (10%). UDC was characterized by at least one readmission or death in the 3 months after inclusion; the mortality rates for this clinical entity were 21% and 36% at 3 months and 1 year, respectively. By definition, all pre-ACLF patients developed ACLF within 3 months after enrollment and had the highest 3-month (54%) and 1-year (67%) mortality rates. Pre-ACLF was characterized by higher prevalence of bacterial infections and higher degree of inflammation, while UDC was characterized by a higher prevalence of surrogates of severe portal hypertension.

In the current issue of the *United European Gastroenterology Journal*, Balcar et al. evaluated the prevalence and outcomes of these subgroups of AD in a large cohort of hospitalized patients with cirrhosis in a tertiary care center.[7] In this study, 210 patients hospitalized for AD without ($n = 173$) or with ACLF ($n = 37$, comparator) were included and followed up for a period of 60 months. Most of the patients with AD (58%) had UDC, while 26% were classified as SDC and 16% as pre-ACLF. Noteworthy, the 3-month and 1-year mortality rates were comparable to those observed in the PREDICT study for pre-ACLF patients (43% and 75%, respectively), but SDC and UDC patients had better outcomes (1-year mortality rates, 7% for SDC and 20% for UDC), probably because most of the patients were included at their first episode of AD. Once again in keeping with the PREDICT study, Balcar et al. found that pre-ACLF patients had higher grade of systemic inflammation compared to SDC and UDC patients, as evidenced by higher levels of C-reactive protein, thus supporting the current hypothesis that systemic inflammation plays a pivotal role in determining the clinical courses of patients with AD.[8]

The study by Balcar et al. had some specific features such as the availability of hepatic venous pressure gradient (HVPG) in a subgroup of patients and long-term follow-up.[7] HVPG was not significantly different in the four groups, suggesting that although portal hypertension is necessary for decompensation, inflammation drives the pattern of decompensation.[8] Balcar et al. found that 22% and 31% of patients with SDC and UDC, respectively, developed ACLF during long-term follow-up, therefore, suggesting that ACLF may occur even in less-risky patients. Finally, the highest long-term mortality rate was observed in pre-ACLF patients suggesting that these patients need an aggressive treatment and early assessment for liver transplant eligibility.

Both PREDICT study and Balcar study classified AD patterns according to subsequent outcomes; however, in clinical practice, it is hard to identify to which pattern the patients with AD belong to. Future studies should address this issue; meanwhile, those with more severe systemic inflammation (e.g., higher C-reactive protein level, bacterial infections) and CLIF-C AD score ≥50 deserve a more aggressive management and an early assessment for liver transplant eligibility.

CONFLICT OF INTEREST

Carmine Gambino and Salvatore Piano have nothing to disclose regarding the content of this manuscript. Salvatore Piano advises Mallinckrodt.

KEYWORDS

ACLF, cirrhosis, liver, hepatology, portal hypertension

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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