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Impact of First and Further Decompensation in Metabolic-Dysfunction Associated Compensated Advanced Chronic Liver Disease

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BACKGROUND

Metabolic dysfunction-associated steatotic liver disease (MASLD) currently stands as one of the foremost global health challenges, with a prevalence of 38% worldwide according to the most recent estimates [1] and with a concerning upward trend due to the parallel anticipated increasing of Diabetes and Obesity epidemic in the coming years [2].

There is a long-standing agreement that the first decompensation - defined as ascites, hepatic encephalopathy (HE), variceal bleeding, and jaundice- appears the pivotal event for patients' prognosis and marks the transition from the compensated, also known as compensated advanced chronic liver disease (cACLD), to the decompensated stage of cirrhosis [3]. Although only a small fraction of patients dies following the first decompensation episode, the risk of developing further decompensation increases and the median survival dramatically decreases [4]. The occurrence of a further decompensation event - defined according to the Baveno VII Consensus [5] as either the recurrence of the initial event or the development of a second decompensation event - represents a crucial turning point in the natural history of the liver disease, markedly increasing the risk of liver-related death (LR-D) in those patients.

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AIM

We assessed the cumulative incidence of first and further (acute and non-acute) decompensation and evaluated their impact on LR-D in patients with compensated advanced chronic liver disease (cACLD) due to metabolic dysfunction-associated steatotic liver disease (MASLD).

METHODS

International multicenter retrospective study (17 centers) on 6,061 consecutive patients with clinical (LSM>10 kPa) or biopsy-proven (F3-F4 fibrosis) diagnosis of cACLD due to MASLD. First and further decompensation were defined according to Baveno VII criteria. Competing risk analyses estimated the cumulative incidence of first and further decompensations, treating liver-related death (LR-D), extra-hepatic death (EH-D), and liver transplantation (LT) as competing events. Cumulative Incidence Functions (CIFs) were compared using Gray's test and stratified by decompensation type and cause of death. Time-to-event analyses were anchored at cACLD diagnosis (first decompensation) and at first decompensation (subsequent events), with 5-year CIFs reported. Cause-specific Cox models with time-dependent covariates assessed the impact of decompensations and HCC on LR-D. Multivariable models included age, sex, diabetes, and liver function markers when available.

A seven-state multistate model estimated transitions from cACLD to better assess the clinical course of cACLD due to MASLD. Analyses were conducted in R (v4.3.3) using cmprsk, mstate, and related packages.

RESULTS

The cumulative incidence of the first decompensation was 3.5% (95% C.I 3.0-4.1) at 5 years, increasing 19-fold the risk of LR-D using Cox analysis (Figure 1A); the cumulative incidence of further decompensation was 43.9% (95% C.I 37.2-50.2) at 5 years among patients with first decompensation (Figure 1A), additionally increasing 1.5-times the risk of LR-D. Ascites, followed by variceal bleeding, were the most common events in both first and further decompensation. Hepatocellular carcinoma (HCC) further independently increased the risk of LR-D by 3- and 1.4-fold in the whole cohort of cACLD due to MASLD and in those who experienced first decompensation, respectively.

CONCLUSIONS

The first and further decompensations represent tipping points in the clinical course of patients with cACLD due to MASLD, increasing 19-times and additionally 1.5-times the risk of LR-D. HCC is an independent predictor of LR-D in patients with cACLD due to MASLD, resulting in an additional risk of LR-D when associated with both first and further decompensation.

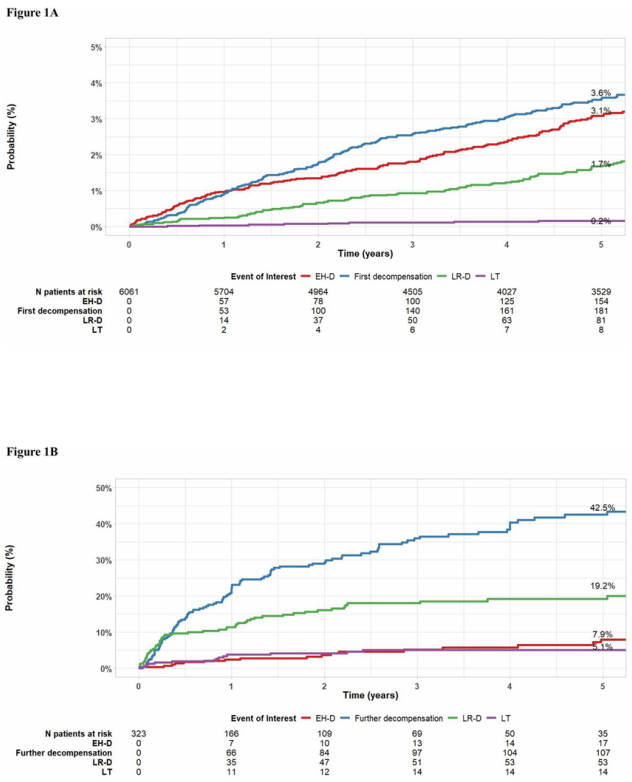

Figure 1. Five-years CIF of major events in the whole cohort of cACLD due to MASLD. (A) Five-years CIF of first decompensation, extra-hepatic death and LT being as competing events. (B) Five-years CIF of first decompensation, extra-hepatic death and LT being as competing events.

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