

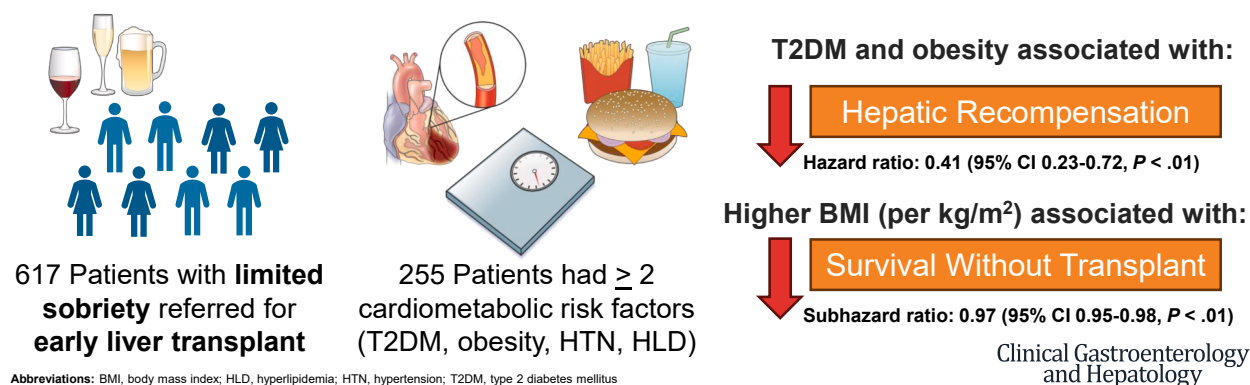
Cardiometabolic Risk Factors Impair Recompensation and Survival in Alcohol-Associated Liver Disease



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BACKGROUND & AIMS:

Patients with alcohol-associated liver disease (ALD) frequently have cardiometabolic risk factors (CMRFs); however, their association with clinical outcomes remains unclear. We assessed the impact of CMRFs on hepatic recompensation and survival for patients referred for early liver transplant (LT) for ALD.

METHODS:

This multicenter, retrospective cohort study assessed patients with ALD and less than 6 months of sobriety from alcohol who were evaluated for early LT. Data on CMRFs, including body mass index (BMI), history of diabetes (T2DM), hypertension (HTN), and hyperlipidemia (HLD), were collected. Primary outcomes were hepatic recompensation and survival without LT.

Abbreviations used in this paper: ACLF, acute-on-chronic liver failure; AH, alcohol-associated hepatitis; aHR, adjusted hazard ratio; ALD, alcohol-associated liver disease; aOR, adjusted odds ratio; AUD, alcohol use disorder; BMI, body mass index; CI, confidence interval; CMRF, cardiometabolic risk factor; HLD, hyperlipidemia; HR, hazard ratio; HTN, hypertension; IQR, interquartile range; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-stage Liver Disease; MetALD, metabolic dysfunction- and alcohol-associated liver disease; RESOLVE-ALD, Recovery, Survival, and

Outcomes in Alcohol Associated Liver Disease; sHR, subdistribution hazard ratio; T2DM, type 2 diabetes mellitus; U.S., United States.

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RESULTS:

Six hundred seventeen patients with a median Model for End-stage Liver Disease (MELD) 3.0 at referral of 27 (interquartile range [IQR], 19–35) were included. A total of 307 patients (50%) were declined for LT or ultimately removed from the waitlist. Having any CMRFs was associated with decreased hepatic recompensation at 6 months (adjusted hazard ratio [aHR], 0.85; 95% confidence interval [CI], 0.74–0.98; $P = .03$), 12 months (aHR, 0.82; 95% CI, 0.70–0.97; $P = .02$), and 24 months (aHR, 0.71; 95% CI, 0.57–0.88; $P < .01$) post LT referral, with T2DM and elevated BMI playing the biggest role. In an adjusted competing risk analysis, higher BMI per kg/m^2 (subdistribution hazard ratio, 0.97; 95% CI, 0.95–0.98; $P < .01$) was associated with decreased survival without LT.

CONCLUSIONS:

CMRFs—particularly T2DM and elevated BMI—were associated with lower recompensation and survival in patients declined for early LT for ALD, even when controlling for disease severity. These findings highlight the importance of considering CMRFs when weighing the potential for recompensation and need for transplantation in patients considered for early LT for ALD.

Keywords: Alcohol-Associated Liver Disease; Alcohol-associated Hepatitis; Liver Transplant; Steatotic Liver Disease.

Alcohol-associated liver disease (ALD) is a leading cause of advanced liver disease globally, and its burden continues to rise with increasing harmful alcohol use.^{1–4} The traditional 6-month abstinence rule for liver transplantation (LT) in ALD is an unreliable predictor of post-transplant outcomes. Moreover, mortality during this waiting period is exceedingly high for patients with elevated Model for End-stage Liver Disease (MELD) scores who are not transplanted.^{5–7} Data suggest that early LT for patients with ALD—including those with alcohol-associated hepatitis (AH) and limited sobriety—improves survival without a disproportionately higher return to alcohol use, leading many transplant centers to adopt early LT practices.^{8–10} However, it is not well-understood how cardiometabolic risk factors (CMRFs) affect survival or recompensation in this specific population.

CMRFs—such as type 2 diabetes mellitus (T2DM), elevated body mass index (BMI), hyperlipidemia (HLD), and hypertension (HTN)—are highly prevalent among adults in the United States (U.S.) and frequently coexist in patients with ALD.¹¹ The recently proposed entity of metabolic dysfunction- and alcohol-associated liver disease (MetALD) highlights this overlap, encompassing patients with moderate alcohol intake and at least 1 CMRF.¹² Understanding the impact of CMRFs in ALD is particularly relevant given growing recognition that metabolic dysfunction and alcohol act synergistically to accelerate the progression of liver disease.^{13–16} For example, individuals consuming fewer than 4 drinks per week with only 1 CMRF demonstrate a 2.2% prevalence of significant fibrosis, whereas those consuming 14 to 35 drinks per week with 4 to 5 CMRFs exhibit a prevalence of 28.6%.¹⁷ Therefore, understanding how CMRFs modify the course of ALD is essential for improving risk stratification.

A population-based study from Spain found that, among patients with heavy alcohol use, metabolic syndrome independently increases liver stiffness, raising

the risk of fibrosis by 4-fold.¹⁸ Similarly, in patients with ALD, both insulin resistance¹⁹ and elevated BMI²⁰ independently predict fibrosis severity. In the National Health and Nutrition Examination Survey III, T2DM and insulin resistance were predictors of overall mortality in ALD, whereas obesity, T2DM, and metabolic syndrome were predictors of liver-specific mortality.²¹

Although metabolic dysfunction appears to worsen outcomes in ALD, its impact in decompensated patients remains underexplored, particularly for those evaluated for early LT.²² Existing research has focused on alcohol use disorder (AUD) and the risk of returning to alcohol use, whereas little is known about how CMRFs influence outcomes in this cohort.¹⁰ Clarifying this relationship may improve prognostication, help identify patients less likely to recover without LT, and guide decision-making regarding transplant and organ allocation. Thus, we aimed to assess the impact of CMRFs on hepatic recompensation and survival without transplant among patients evaluated for early LT for ALD. Additionally, we evaluated secondary outcomes including post-LT mortality, need for retransplantation, and risk of rejection to better characterize the effect of CMRFs on transplant outcomes in this unique cohort of patients with limited sobriety.

Patients and Methods

Study Population and Design

This multicenter, retrospective cohort study of 6 LT centers in the Recovery, Survival, and Outcomes in Alcohol Associated Liver Disease (RESOLVE-ALD) consortium assessed adult patients with ALD and less than 6 months of sobriety from alcohol who were evaluated for early LT between 2018 and 2021. RESOLVE-ALD is a group of LT centers in the U.S., including University of California San Diego, Stanford University, University of Massachusetts, University of Minnesota, Northwestern

University, and University of North Carolina. Each site utilized its own protocol for LT evaluation and selection, but all sites offered early LT for AH and acute-on-chronic liver failure (ACLF) or cirrhosis from ALD (Supplementary Table 1).²³ The definition of AH was based on the National Institute on Alcohol Abuse and Alcoholism criteria of consuming greater than 40 to 60 grams of alcohol per day with less than 60 days of abstinence prior to the onset of jaundice, serum bilirubin >3 mg/dL, aspartate aminotransaminase 50 to 400 IU, and aspartate aminotransaminase to alanine aminotransferase ratio >1.5.¹¹

Patients with either AH or cirrhosis from ALD and less than 6 months of sobriety were included in the study. Period of sobriety was defined as date of last drink to date of LT referral. Patients with prior LT or who were considered for simultaneous liver and kidney transplant were excluded. The study was conducted in accordance with both the Declarations of Helsinki and Istanbul. Ethics approval for this study was provided by each institution's Institutional Review Board and shared via a data use agreement.

Definition of Variables

Data were retrospectively collected from electronic medical records at each center from chart review of notes and laboratory values at the time of LT referral. The following variables were collected: demographic and psychosocial information, including age, sex, race, education, employment, social support, insurance type, alcohol and substance use history, and mental health history; disease-specific information, including decompensation events, MELD 3.0 score, Child-Pugh Class score, and AH status; and CMRFs, including BMI, history of T2DM, HTN, HLD, or prior weight loss surgery. A patient was defined as having T2DM, HTN, or HLD based on extensive chart review of notes, problem lists, and prior or current medications. Elevated BMI was defined as BMI greater than 25 kg/m². A composite variable was created to assess CMRFs including T2DM, elevated BMI, HTN, and HLD.

Data on biopsy-proven rejection (early vs late acute cellular rejection, early vs late antibody mediated rejection, or chronic rejection), post-LT infection, and need for retransplantation were collected for patients who received LT. For patients who were not transplanted, hepatic decompensation events and MELD 3.0 scores were collected at 6, 12, and 24 months following initial LT referral. Data on mortality and return to alcohol use were collected for all patients. Follow-up time was calculated from the date of referral for LT to death, transplant, or last alive date, whichever occurred first.

Primary and Secondary Outcomes

The primary outcomes of the study were hepatic recompensation and survival without LT. Hepatic

What You Need to Know

Background

Patients with advanced alcohol-associated liver disease referred for liver transplantation frequently have cardiometabolic risk factors, but their association with clinical outcomes in patients with limited sobriety remains unclear.

Findings

Cardiometabolic risk factors—primarily type 2 diabetes mellitus and obesity—are associated with decreased hepatic recompensation and survival without transplant for patients with limited sobriety (<6 months).

Implications for patient care

Patients with advanced alcohol-associated liver disease who have type 2 diabetes mellitus and obesity may need to be prioritized in the early liver transplant context due to decreased capacity for recompensation and survival.

recompensation was defined as survival without LT and the absence of further decompensation events, including: ascites requiring diuretics or paracentesis; hepatic encephalopathy requiring medication; or variceal or portal hypertensive bleeding, as determined by endoscopy, the need for transjugular intrahepatic portosystemic shunt, or the use of octreotide. Secondary outcomes were post-LT mortality, need for retransplantation, and rejection.

Statistical Analysis

Descriptive characteristics of patients with CMRFs were compared with those without risk factors using χ^2 analysis for binary variables, *t*-test for continuous variables with normal distribution, or Mann-Whitney *U* test for nonparametric data. Cox proportional hazards models, logistic regression, and Fine-Gray competing risk regression (with LT as competing risk) were used to assess for the primary and secondary outcomes. Statistical analyses were performed using STATA, and statistical significance was defined as *P* < .05.

Results

Demographic and Psychosocial Characteristics at Time of Referral

There were 617 patients included in the study, with a median MELD of 3.0 at time of referral of 27 (interquartile range [IQR], 19–35). The mean age was 49 ± 11 years; 243 patients (39%) were female, and 87 (14%) identified as Hispanic/Latino. A total of 327 patients

(53%) had decompensated cirrhosis due to ALD and 283 (46%) had AH; data for this variable were unavailable for 7 patients (1%). Median time from last drink to referral was 79 days (IQR, 34–130 days), and 82 patients (13%) had return to alcohol use after referral. One-third of those who had return to alcohol use were classified as slips and not sustained heavy use (Table 1).

Three hundred fifty-four patients (57%) were waitlisted for LT, and 243 (39%) were ultimately transplanted. Of those transplanted, 112 (46%) met

criteria for AH. Among the 307 patients who were declined for LT or removed from the waitlist after initial listing, the reasons for decline included: high risk of return to alcohol use (37%), lack of social support (6%), medically too well (26%), medically too sick or died (13%), or other (18%). Reasons given for “other” included financial or insurance complications, loss to follow-up, patient request for waitlist removal, relocation out of state, or substance use (Figure 1).

Table 1. Baseline Demographic, Psychosocial, and Clinical Characteristics by Number of CMRFs

Characteristics	All patients N = 617	0 to 1 CMRFs n = 362	2+ CMRFs n = 255	P value
Demographics				
Mean age, y	49 (11)	47 (11)	51 (11)	<.01
Female	243 (39)	170 (46)	73 (29)	<.01
Race/ethnicity				.01
White	489 (79)	299 (83)	190 (75)	
Hispanic/Latino	87 (14)	37 (10)	50 (20)	
Black	14 (2)	9 (2)	5 (2)	
Asian	9 (2)	3 (1)	6 (2)	
Other/mixed race	18 (3)	14 (4)	4 (1)	
Level of education				.83
Grade/middle school	25 (4)	12 (3)	13 (5)	
High school or GED	213 (35)	123 (34)	90 (35)	
Some college/AA/bachelor's	299 (49)	176 (49)	123 (49)	
Graduate degree	45 (7)	29 (8)	16 (6)	
Other	35 (5)	22 (6)	13 (5)	
Employed	289 (47)	155 (43)	134 (53)	<.01
Insurance type				.08
Private	324 (53)	186 (51)	138 (54)	
Public	271 (44)	158 (44)	113 (44)	
Other	22 (3)	18 (5)	4 (2)	
Psychosocial factors				
Married/partnership	343 (56)	193 (53)	150 (59)	<.01
Tobacco use	175 (29)	107 (30)	68 (27)	.45
Cannabis use	116 (19)	72 (20)	44 (17)	.79
Other substance use	137 (22)	74 (20)	63 (25)	.57
Psychiatric diagnosis	345 (56)	200 (55)	145 (57)	.69
>10 standard drinks/d	267 (43)	154 (43)	113 (44)	.80
Time from last drink to referral, d	79 (34–130)	77 (33–129)	81 (36–130)	.85
Return to alcohol use after referral	82 (13)	54 (15)	28 (11)	.19
Liver disease history				
MELD 3.0 at referral	27 (19–35)	27 (20–35)	27 (19–34)	.55
Diagnosis of AH	283 (46)	183 (51)	100 (39)	<.01
History of HCC	43 (7)	22 (6)	21 (8)	.38
Prior hepatic decompensation				
Ascites	550 (89)	323 (89)	227 (89)	.94
Hepatic encephalopathy	462 (75)	265 (73)	197 (77)	.25
Variceal bleeding	104 (17)	56 (15)	48 (19)	.27
CMRFs				
BMI, kg/m ²	28 (24–33)	25 (23–30)	30 (27–35)	<.01
T2DM	118 (19)	9 (2)	109 (43)	<.01
HTN	265 (43)	43 (12)	222 (87)	<.01
HLD	102 (17)	7 (2)	95 (37)	<.01
Weight loss surgery	55 (9)	33 (9)	22 (9)	.83

NOTE. Data are presented as mean (standard deviation) or median (interquartile range) for continuous variables, and number (%) for categorical variables.

NOTE. Boldface P values indicate statistical significance ($P < .05$).

AA, associate of arts; AH, alcohol-associated hepatitis; BMI, body mass index; CMRFs, cardiometabolic risk factors; GED, general educational development; HCC, hepatocellular carcinoma; HLD, hyperlipidemia; HTN, hypertension; MELD, Model for End-stage Liver Disease; T2DM, type 2 diabetes mellitus.

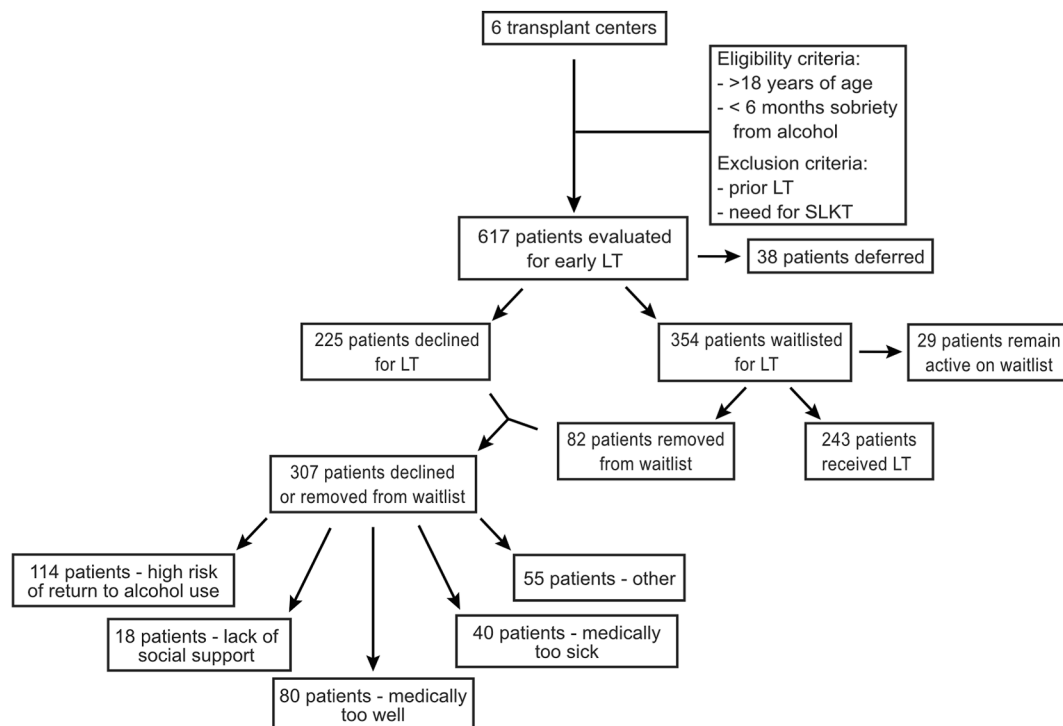


Figure 1. Diagram depicting patients evaluated for LT and outcomes of evaluation including number of patients waitlisted, deferred, or ultimately transplanted and reasons for decline and/or removal from the waitlist. SLKT, simultaneous liver-kidney transplant.

CMRFs at Time of Referral

The prevalence of T2DM, HTN, and HLD in the cohort was 19%, 43%, and 17%, respectively, and the median BMI was 28 kg/m² (IQR, 24–33 kg/m²). Among patients with AH, the prevalence of T2DM, HTN, and HLD was slightly lower at 14%, 38%, and 12%, respectively ($P < .01$, $P = .02$, and $P < .01$), but the median BMI was the same at 28 kg/m² (IQR, 25–34 kg/m²). Two hundred fifty-five patients (41%) had 2 or more CMRFs. A small subset of patients (9%) had a history of bariatric surgery: 18 reported prior gastric sleeve and 37 reported prior Roux-en-Y gastric bypass (Table 1).

Patients with 2 or more CMRFs were more likely to be older (51 vs 47 years; $P < .01$), male (71% vs 54%; $P < .01$), Hispanic/Latino (20% vs 10%; $P = .01$), employed (53% vs 43%; $P < .01$), and married or in a long-term partnership (59% vs 53%; $P < .01$). There was no difference in median MELD 3.0 score at referral (27 vs 27; $P = .55$), median time from last drink to referral (81 vs 77 days; $P = .85$), or return to alcohol use after referral (11% vs 15%; $P = .19$) between patients with 2 or more CMRFs and those with 0 or 1 CMRFs. However, patients with 2 or more CMRFs were less likely to meet criteria for AH (39% vs 51%; $P < .01$) (Table 1).

Hepatic Recompensation Without Liver Transplant

Adjusted for age, sex, race, and MELD 3.0 score, the presence of CMRFs (T2DM, elevated BMI, HTN, and

HLD) was associated with decreased hepatic recompensation at 6 months (adjusted hazard ratio [aHR], 0.85; 95% confidence interval [CI], 0.74–0.98; $P = .03$), 12 months (aHR, 0.82; 95% CI, 0.70–0.97; $P = .02$), and 24 months (aHR, 0.71; 95% CI, 0.57–0.88; $P < .01$) after initial LT referral. Patients with both T2DM and elevated BMI had significantly decreased hepatic recompensation at 6 months (aHR, 0.53; 95% CI, 0.31–0.89; $P = .02$), 12 months (aHR, 0.41; 95% CI, 0.23–0.72; $P < .01$), and 24 months (aHR, 0.27; 95% CI, 0.12–0.57; $P < .01$) (Figure 2A) compared with those without T2DM or elevated BMI. When comparing patients with AH with those with decompensated ALD (non-AH), there were similar findings of decreased recompensation at 6, 12, and 24 months for patients with T2DM and elevated BMI, as well as for patients with any CMRFs (Supplementary Table 2).

Patients with 2 or more CMRFs were significantly less likely to have recompensation over 24 months compared with patients with 0 or 1 risk factors (aHR, 0.59; 95% CI, 0.36–0.97; $P = .04$) (Figure 2B). HTN and HLD were not significant predictors of hepatic recompensation on their own at 6, 12, or 24 months in an adjusted analysis (Table 2). History of weight loss surgery was also not significantly associated with recompensation at 6 months (aHR, 1.12; 95% CI, 0.67–1.89; $P = .67$), 12 months (aHR, 0.93; 95% CI, 0.51–1.70; $P = .82$), or 24 months (aHR, 1.62; 95% CI, 0.58–4.52; $P = .36$).

Return to alcohol use after referral for LT was a significant predictor of decreased hepatic recompensation at 6 months (hazard ratio [HR], 0.35; 95% CI, 0.25–0.47;

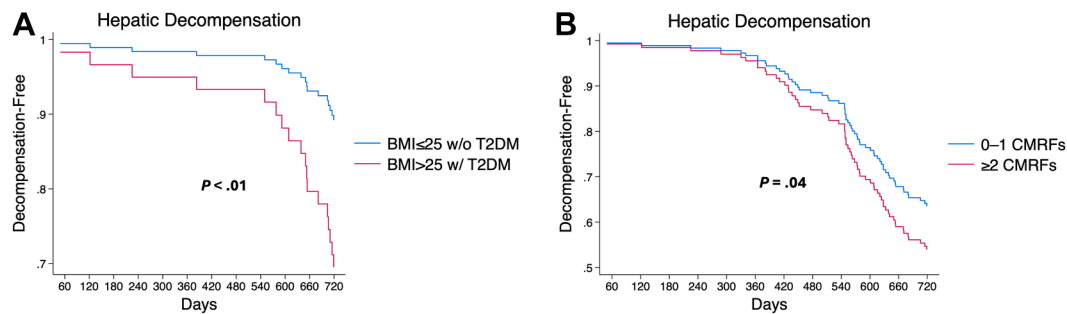


Figure 2. Kaplan-Meier curves of hepatic decompensation over 24 months post-referral for liver transplant. (A) Patients with and without T2DM and elevated BMI. (B) Patients with 0 or 1 CMRFs vs 2 or more CMRFs.

$P < .01$), 12 months (HR, 0.31; 95% CI, 0.22–0.43; $P < .01$), and 24 months (HR, 0.30; 95% CI, 0.20–0.45; $P < .01$). There was no significant association between return to alcohol use and having any CMRFs (adjusted odds ratio [aOR], 1.00; 95% CI, 0.80–1.27; $P = .97$), T2DM alone (aOR, 0.84; 95% CI, 0.42–1.66; $P = .61$), or elevated BMI alone (aOR, 0.92; 95% CI, 0.55–1.54; $P = .75$).

Survival Without LT

Two hundred two patients had survival without LT over a median follow-up of 708 days (IQR, 422–1016 days). In a Fine-Gray competing risk analysis adjusting

for age, sex, race, and MELD 3.0 score at referral, higher BMI (per kg/m^2) was associated with decreased survival (subdistribution hazard ratio [sHR], 0.97; 95% CI, 0.95–0.98; $P < .01$) (Figure 3A). However, this finding was no longer significant when the analysis was restricted to patients with return to alcohol use (sHR, 1.01; 95% CI, 0.87–1.07; $P = .55$). There was also a nonsignificant decrease in survival among patients with T2DM and elevated BMI (sHR, 0.70; 95% CI, 0.42–1.16; $P = .16$) (Figure 3B) and in patients with a history of weight loss surgery (sHR, 0.63; 95% CI, 0.38–1.05; $P = .08$) in an adjusted analysis. Patients with return to alcohol use after referral had significantly decreased survival without transplant (sHR, 0.39; 95% CI, 0.24–0.62; $P < .01$).

Table 2. Hepatic Recompensation at 6, 12, and 24 Months by CMRFs

	aHR (95% CI)	P value (adjusted)
Hepatic recompensation at 6 mo		
BMI >25 kg/m^2	0.66 (0.48–0.91)	.01
T2DM	0.70 (0.46–1.05)	.09
HTN	0.98 (0.72–1.33)	.88
HLD	0.80 (0.52–1.23)	.31
T2DM + BMI >25 kg/m^2	0.53 (0.31–0.89)	.02
Any CMRF	0.85 (0.74–0.98)	.03
Hepatic recompensation at 12 mo		
BMI >25 kg/m^2	0.60 (0.41–0.86)	<.01
T2DM	0.61 (0.39–0.96)	.03
HTN	0.92 (0.65–1.31)	.64
HLD	0.92 (0.57–1.49)	.73
T2DM + BMI >25 kg/m^2	0.41 (0.23–0.72)	<.01
Any CMRF	0.82 (0.70–0.97)	.02
Hepatic recompensation at 24 mo		
BMI >25 kg/m^2	0.72 (0.45–1.15)	.17
T2DM	0.38 (0.21–0.68)	<.01
HTN	0.72 (0.46–1.11)	.14
HLD	0.57 (0.32–1.02)	.06
T2DM + BMI >25 kg/m^2	0.27 (0.12–0.57)	<.01
Any CMRF	0.71 (0.57–0.88)	<.01

NOTE. HR adjusted for age, sex, race, and MELD 3.0 score at 6, 12, and 24 months post-liver transplant referral.

NOTE. Bolded values are statistically significant with $P < .05$.

aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; CMRF, cardiometabolic risk factor; HLD, hyperlipidemia; HTN, hypertension; MELD, Model for End-stage Liver Disease; T2DM, type 2 diabetes mellitus.

Waitlist and Post-LT Outcomes

There was no difference in adjusted odds of receiving a LT (aOR, 1.07; 95% CI, 0.92–1.23; $P = .38$) or being declined from the waitlist (aOR, 0.92; 95% CI, 0.79–1.07; $P = .28$) for patients with CMRFs compared with those without CMRFs (model adjusted for age, sex, race, and MELD 3.0 score at referral). A total of 21 patients (9%) died post-LT, with no significant difference in survival for patients with CMRFs (aHR, 0.75; 95% CI, 0.49–1.14; $P = .17$). Six patients required a repeat LT, with a nonsignificant increase among those with any CMRFs (aHR, 2.06; 95% CI, 0.91–4.64; $P = .08$). Eighty patients had evidence of post-LT rejection (both acute cellular and antibody-mediated rejection), with no difference by CMRF profile (aHR, 1.05; 95% CI, 0.84–1.33; $P = .65$) (Table 3).

Eighty patients (33%) experienced a post-LT infection: 73 bacterial, 5 viral, and 2 fungal. Patients with post-LT infections were significantly less likely to survive (aHR, 0.32; 95% CI, 0.13–0.78; $P = .01$) but were not more likely to have T2DM (aHR, 0.88; 95% CI, 0.47–1.65; $P = .70$) or elevated BMI (aHR, 0.97; 95% CI, 0.94–1.01; $P = .14$). Return to alcohol use post-LT was seen in 37 patients (15%), with 19 (8%) categorized as sustained use. Patients with return to alcohol use post-LT did not have a significant decrease in short-term survival (aHR, 0.50; 95% CI, 0.44–1.58; $P = .58$).

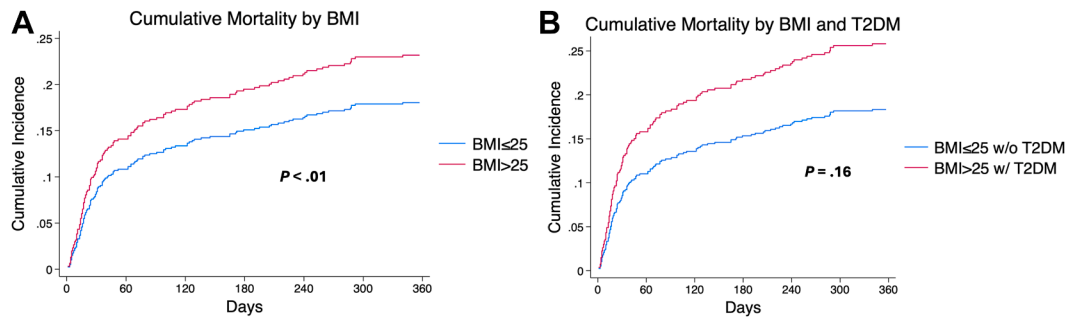


Figure 3. (A) Cumulative incidence of mortality by BMI. (B) Cumulative incidence of mortality by BMI and T2DM status.

Table 3. Transplant Status, Decline From Waitlist, and Post-LT Outcomes by CMRFs

	aOR (95% CI)	P value (adjusted)
Transplanted		
BMI >25 kg/m ²	1.02 (0.71–1.47)	.93
T2DM	1.25 (0.81–1.91)	.31
HTN	1.17 (0.82–1.66)	.39
HLD	1.09 (0.69–1.74)	.70
T2DM + BMI >25 kg/m ²	1.09 (0.84–1.42)	.52
Any CMRF	1.07 (0.92–1.23)	.38
Declined from waitlist		
BMI >25 kg/m ²	0.82 (0.58–1.17)	.28
T2DM	0.92 (0.61–1.40)	.71
HTN	0.91 (0.65–1.28)	.58
HLD	0.84 (0.54–1.32)	.45
T2DM + BMI >25 kg/m ²	0.88 (0.68–1.13)	.32
Any CMRF	0.92 (0.79–1.07)	.28
	aHR (95% CI)	P value (adjusted)
Post-LT survival		
BMI >25 kg/m ²	0.58 (0.19–1.75)	.34
T2DM	0.74 (0.26–2.08)	.57
HTN	0.91 (0.37–2.22)	.82
HLD	0.44 (0.16–1.18)	.10
T2DM + BMI >25 kg/m ²	0.68 (0.33–1.37)	.28
Any CMRF	0.75 (0.49–1.14)	.17
Post-LT rejection		
BMI >25 kg/m ²	1.63 (0.95–2.79)	.08
T2DM	1.13 (0.62–2.06)	.70
HTN	0.71 (0.44–1.14)	.16
HLD	1.34 (0.73–2.46)	.34
T2DM + BMI >25 kg/m ²	1.32 (0.91–1.93)	.14
Any CMRF	1.05 (0.84–1.33)	.65
Need for retransplant		
BMI >25 kg/m ²	0.93 (0.16–5.23)	.93
T2DM	3.42 (0.52–22.35)	.20
HTN	4.34 (0.59–32.05)	.15
HLD	3.96 (0.66–23.75)	.13
T2DM + BMI >25 kg/m ²	1.71 (0.42–7.01)	.46
Any CMRF	2.06 (0.91–4.64)	.08

NOTE. ORs and HRs adjusted for age, sex, race, and MELD 3.0 score at time of referral for liver transplant.

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; CMRF, cardiometabolic risk factor; HLD, hyperlipidemia; HTN, hypertension; LT, liver transplant; T2DM, type 2 diabetes mellitus.

Discussion

Main Findings

Even when controlling for disease severity, CMRFs were associated with decreased hepatic recompensation and survival without LT in patients evaluated for early LT for ALD. The negative impact was most pronounced in those with T2DM and elevated BMI. When comparing patients with AH with those with decompensated ALD (non-AH), the association between CMRFs and decreased hepatic recompensation remained consistent, suggesting that the findings are not overly influenced by the greater capacity of patients with AH to recompensate with sobriety. Overall, these findings are likely due to patients with ALD and CMRFs having a reduced ability to recompensate from the synergistic effects of alcohol and metabolic dysfunction, leading to impaired hepatic and systemic recovery. The presence of metabolic dysfunction may also increase risk of infections, which could have contributed to worse outcomes.²⁴

We also found that return to alcohol use was a significant negative predictor of both recompensation and survival without transplant. There was no association between return to alcohol use and CMRF status; however, return to alcohol use may act as an effect modifier, as the association between higher BMI and decreased survival was no longer significant when the analysis was restricted to patients with return to alcohol use. Of note, the majority of patients in our study did not return to alcohol use after LT referral.

Among patients who were transplanted, there was no difference in survival or rates of rejection between those with and without CMRFs. Patients with return to alcohol use post-LT did not have a significant decrease in survival; however, this finding may have been affected by the length of follow-up in our study and the fact that only 8% of patients had sustained or heavy alcohol use post-LT. Overall, patients with CMRFs were waitlisted and transplanted at similar rates to those without risk factors, supporting parity in access to and allocation of livers for patients with metabolic syndrome.

In Context With Current Literature

Prior studies have focused mainly on return to alcohol use post-LT and survival for patients with limited sobriety.^{8,25} Compared with a 2023 study of patients with AH who were declined for early LT, our study found a higher rate of hepatic recompensation, which may be due to the inclusion of patients with cirrhosis or ACLF from ALD in addition to AH in our cohort.²⁵ We observed comparable short-term survival (54%) for patients declined for early LT as prior studies.^{5,25} Similar to the ACCELERATE-AH study, we found a low mortality rate post-LT (9%) and low rate of return to alcohol use post-LT (15%), supporting continued use of early LT protocols for patients with ALD and limited sobriety.⁸

A prior multicenter cohort study of patients undergoing LT demonstrated decreased post-LT survival for patients with concomitant T2DM and obesity but did not specifically look at patients with ALD and limited sobriety or outcomes for those not transplanted.²⁶ Our study is unique in analyzing the effect of CMRFs on survival and recompensation without transplant in the context of limited sobriety, adding important considerations to clinical practice where the decision regarding transplantation must consider the potential for spontaneous recovery.

It is well-documented that the leading cause of death in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) is cardiovascular disease, and that MASLD is an independent risk factor for cardiovascular events.²⁷ In contrast, patients with MetALD or ALD are more likely to die from liver-related complications.^{28–30} Although it was not the primary focus of our study, cause-of-death data showed that the majority of patients died from liver-related complications, consistent with prior studies in which liver-related mortality predominates among patients with ALD.

Implications for Clinical Care and Research

Our findings suggest a possible worse prognosis for patients with ALD and CMRFs who are not ultimately transplanted. This highlights the need for pre-LT risk stratification to determine optimal timing of LT for this specific cohort. If patients with ALD and CMRFs have less capacity for recompensation or survival, they may need to be prioritized in the early LT context. Given that insulin resistance and obesity appear to be key drivers of poor outcomes in our cohort, further research into pharmacologic therapies targeting these pathways may clarify whether patients with ALD and CMRFs could benefit from interventions originally developed for patients with MASLD. The high prevalence of CMRFs in patients with ALD underscores the importance of including this population in clinical trials. Long-term post-LT studies are also needed to understand if there are differences in outcomes beyond the initial post-LT period.

Strengths and Limitations

A major strength of the study is that it includes 6 transplant centers across the country, which not only increases the power and generalizability of the findings, but also more accurately captures the diversity of the U.S. compared with single-center or smaller cohort studies. We were able to obtain granular data on a multitude of patient factors, allowing the consortium to evaluate multiple aspects of early LT. One limitation is the retrospective design, which restricts analysis to the data collected by each site. However, our median follow-up periods of 708 days for those who were not transplanted, and 894 days for those who were transplanted, allowed us to examine both short- and medium-term outcomes.

Another limitation is the lack of data regarding the duration of T2DM and glycemic control, which can influence progression of liver and cardiovascular disease. The retrospective nature of the study may limit the sensitivity of capturing patients with prior CMRFs or diet-controlled T2DM or HLD. Additionally, although we collected data on infections in post-LT patients, we do not have infection data for patients who were not transplanted, limiting our ability to assess the impact of infections on those outcomes. Finally, because alcohol consumption itself can influence the development of CMRFs such as HTN and HLD, we looked at both individual and composite risk factors.¹⁴

Conclusion

This study of patients evaluated for early LT for acute ALD from 6 academic LT centers demonstrated that CMRFs negatively affected hepatic recompensation and survival without LT, even when controlling for disease severity. T2DM and elevated BMI seemed to have the greatest impact, likely due to their effects on hepatic inflammation and fibrosis. Return to alcohol use negatively influenced recompensation and may act as an effect modifier for survival without transplant. There were no clear differences in post-LT outcomes among those who were transplanted, highlighting the need for timely transplantation given the limited capacity for spontaneous recovery among patients with CMRFs—particularly T2DM and elevated BMI—and limited sobriety. These findings support a potential contribution of metabolic dysfunction and steatohepatitis to disease progression in patients with ALD and limited sobriety who are evaluated for early LT.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2026.02.001>.

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Data Availability

Deidentified data, analytic methods, and study materials will be made available upon request.