United European Gastroenterology Journal

WILEY | ueg journal

ORIGINAL ARTICLE OPEN ACCESS

Alcohol Use After TIPS Implantation Significantly Increases the Risk of ACLF and Liver-Related Death

Caroline Schwarz[1] | Andrea Kornfehl[2,3] | Reema Abid[2] | Theresa Müllner-Bucsics[2,3,4] | Julia Kappel[2,3,4] | Michael Schwarz[5] | Benedikt S. Hofer[2,3,4,6] | Nina Dominik[2,3,4] | Georg Kramer[2,3,4,6] | Benedikt Simbrunner[2,3,4,6] | Mathias Jachs[2,3,6] | Lukas Reider[7] | Michael Trauner[2,3,4] | Mattias Mandorfer[2,3,4] | Thomas Reiberger[2,3,4,6] | Lukas Hartl[2,3,4]

[1]Department of Internal Medicine IV, Klinik Ottakring, Vienna, Austria | [2]Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria | [3]Vienna Hepatic Hemodynamic Lab, Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria | [4]Clinical Research Group MOTION, Medical University of Vienna, Vienna, Austria | [5]Department of Internal Medicine II, University Clinic of St. Poelten, St. Poelten, Austria | [6]Christian Doppler Lab for Portal Hypertension and Liver Fibrosis, Medical University of Vienna, Vienna, Austria | [7]Division of Interventional Radiology, Department of Radiology, Medical University of Vienna, Vienna, Austria

Correspondence: Thomas Reiberger (thomas.reiberger@meduniwien.ac.at)

Received: 21 April 2025 | **Revised:** 1 October 2025 | **Accepted:** 7 October 2025

Keywords: alcohol use | alcohol-related liver disease | portal hypertension | transjugular intrahepatic portosystemic shunt

ABSTRACT

Background: Complications related to portal hypertension (PH) in patients with alcohol-related liver disease (ALD) can be controlled by transjugular intrahepatic portosystemic shunt (TIPS) placement; however, the impact of ongoing alcohol use (AU) after TIPS remains scarcely investigated.

Methods: ALD patients undergoing TIPS implantation between 2000 and 2022 were included. Laboratory/demographic parameters and clinical events/outcomes were compared per post-TIPS AU status and to a group of $n = 55$ decompensated ALD patients with ongoing AU who did not receive TIPS.

Results: Overall, 248 TIPS patients (78.2% male; median age: 55.5 years; ascites: 69.8%; median MELD: 12), including 90 (36.3%) with ongoing AU after TIPS were included. AU post-TIPS was independently associated with ACLF (asHR 2.27; 95% CI 1.40–3.66; $p < 0.001$) and liver-related death (asHR 1.68; 95% CI 1.05–2.67; $p = 0.030$) among patients undergoing TIPS in adjusted multivariable competing risks analysis. When comparing matched decompensated AU patients treated versus non-treated by TIPS, multivariable competing risks regression revealed MELD (asHR 1.07; 95% CI 1.01–1.13; $p = 0.033$) but not TIPS use (asHR 0.70; 95% CI 0.45–1.10; $p = 0.120$) as independent risk factors for ACLF, despite TIPS patients having higher levels of systemic inflammation (CRP).

Conclusion: Post-TIPS AU was frequent and an independent risk factor for ACLF and liver-related death, underlining the importance of interdisciplinary measures supporting alcohol abstinence. TIPS should still not be withheld from ALD patients developing PH complications, since it does not predispose them to ACLF and may prevent liver-related death.

1 | Introduction

The development of portal hypertension (PH) in patients with advanced chronic liver disease (ACLD) is associated with an increased risk for hepatic decompensation and complications such as ascites, variceal hemorrhage, hepatorenal syndrome-type of acute kidney injury (HRS-AKI), and spontaneous bacterial peritonitis (SBP) [1–3]. First as well as further hepatic decompensation are associated with a substantial deterioration in outcome and survival; therefore, prevention of decompensation,

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2025 The Author(s). *United European Gastroenterology Journal* published by Wiley Periodicals LLC on behalf of United European Gastroenterology.

Key Summary

- Transjugular intrahepatic portosystemic shunt (TIPS) placement is an effective therapeutic option in patients with decompensated liver cirrhosis.
- Despite the high prevalence of alcohol-related liver disease, the impact of ongoing alcohol use (AU) after TIPS has not been studied before.
- Patients with ongoing AU had a significantly higher risk of acute-on-chronic liver failure (ACLF) and liver-related death after TIPS placement compared to those who remained abstinent.
- Among matched decompensated AU patients managed with versus without TIPS, only MELD but not TIPS use was an independent risk factor for ACLF according to multivariable competing risks regression.

optimized treatment of decompensation events, and achievement of recompensation have become paramount goals in liver care [2, 4–7].

Non-selective betablockers (NSBB) without and with band ligation represent the standard of care for primary and secondary prophylaxis of portal hypertensive esophageal variceal bleeding, respectively, and may reduce the risk for hepatic decompensation in patients with compensated cirrhosis and clinically significant portal hypertension (CSPH) [1, 4, 8, 9]. In patients with ascites, diuretic treatment and large-volume paracentesis represent the primary therapeutic approach [2, 4, 9].

In the event of severe PH complications such as variceal rebleeding and/or refractory ascites despite optimal management according to the standard of care, the recommended treatment is transjugular intrahepatic portosystemic shunt (TIPS) implantation [2, 4, 10, 11]. TIPS placement has been shown to substantially reduce rebleeding rates in Child-Pugh (CP) C and in CP-B patients with active variceal bleeding during endoscopy, if applied preemptively (i.e., within 72h hours, “early”/“preemptive TIPS”) [12, 13]. In patients with refractory variceal bleeding, TIPS implantation was associated with improved short- and long-term survival, and outperformed emergency esophageal stenting regarding control of bleeding and prevention of rebleeding (“rescue TIPS”) [14]. The decrease in portal pressure induced by TIPS placement also leads to better control or even resolution of ascites in patients with decompensated cirrhosis, thereby reducing the risk of HRS-AKI and SBP [10]. Overall, TIPS implantation was found to prevent further decompensation and improve survival in patients with cirrhosis and PH [15]. Hence, all liver transplant candidates with PH should be evaluated for TIPS implantation as TIPS may serve as a bringing therapy to or even circumvent the need for transplantation [16, 17].

Alcohol-related liver disease (ALD) is the most common underlying etiology for ACLD requiring TIPS implantation in the Western world and one of the most common indications for liver transplantation (OLT) [3, 18, 19]. Although it has been clearly demonstrated that prognosis of ALD-associated PH may be significantly improved by alcohol abstinence even in advanced stages of PH [20], alcohol relapse - even after longer periods of successful abstinence - represents a relevant problem in patients with alcohol-related cirrhosis and those receiving OLT for ALD-related ACLD [21].

However, despite the known negative impact of alcohol use (AU) in ALD-related cirrhosis and after liver transplantation for ALD, data on the consequences of ongoing or recurrent AU in patients who underwent TIPS implantation for complications of ALD-related PH currently remain scarce [19, 22, 23]. Therefore, in this retrospective study, we aimed to investigate the impact of ongoing or recurrent hazardous AU in a Viennese cohort of ALD patients who underwent TIPS placement.

2 | Methods

2.1 | Study Design and Patient Cohort

The aim of this study was to investigate the effect of AU after TIPS placement in terms of outcome and survival among patients with ALD-associated cirrhosis. We assessed consecutive patients who underwent implantation of self-expandable polytetrafluorethylene-covered TIPS for refractory ascites or/and variceal hemorrhage due to ALD-associated cirrhosis between 2000 and 2022 at two tertiary care centers in Vienna, Austria.

The design of the study was a retrospective analysis of a study population that consisted of (i) patients with sufficient follow-up deriving from a cohort that was collected for other purposes in a prospective way (AUTIPS study, NCT03409263: 01/2017 to 11/2022; $n = 32$), (ii) and a retrospective cohort (09/2000 to 09/2019, $n = 216$). The inclusion criteria comprised the following: (i) established diagnosis of ALD cirrhosis, (ii) TIPS indication due to recurrent/refractory ascites or/and variceal hemorrhage, (iii) age $\geq$ 18 years. Individuals with malignancies including hepatocellular carcinoma (HCC) as well as those with a follow-up period $<$ 90 days were excluded to facilitate discrimination between AU-related and non-AU-related events, which was the objective of the study, as opposed to other confounding factors.

Clinical outcomes of patients who continued to consume alcohol after TIPS implantation were compared to another cohort of patients treated at our center with ALD-related decompensated ACLD (dACLD) and ongoing AU who did not undergo TIPS implantation [20]. To ensure comparability with the subgroup who did undergo TIPS and to avoid skewing the non-TIPS cohort toward healthier patients, only individuals with a hepatovenous pressure gradient (HVPG) $\geq$ 16mmHg were included in this group. In this comparison cohort, decompensation was defined as the occurrence of either ascites and/or variceal hemorrhage with or without simultaneous hepatic encephalopathy (HE). Patients in whom HE was the only decompensation event were excluded.

2.2 | Data Acquisition

Demographic and clinical data were retrieved from patients' medical records. Laboratory parameters were acquired through

the respective digital patient data management systems. Data concerning the TIPS procedure were derived from the intervention reports of the respective centers. Mortality data were retrieved from medical records and/or from the Austrian death registry.

2.3 | Parameters and Definitions

Decompensation events (ascites, variceal hemorrhage, hepatic encephalopathy), complications (SBP, other bacterial infections, acute-on-chronic liver failure [ACLF]), OLT, HCC, and death after TIPS implantation including the respective follow-up times were assessed according to clinical documentation [2, 24]. Laboratory parameters for the calculation of CP score and MELD score as well as full blood count and C-reactive protein (CRP) were recorded.

2.4 | Assessment of Alcohol Use

AU was assessed according to patients' reporting, (repeated) serum ethanol levels if available, and clinical documentation of the treating physician [25]. As per the standard protocol at our institution, patients undergoing TIPS were seen at the outpatient clinic every 3 months following TIPS implantation and were specifically asked about their AU behavior by their treating physician during each visit. Likewise, patients with ALD-related decompensated cirrhosis who did not undergo TIPS implantation routinely presented for outpatient clinical visits every 3 months. AU according to patients' reports during these routine visits was documented in their digital medical file by the treating physician. For patients with ALD-related cirrhosis who did or did not undergo TIPS and who were admitted for inpatient care, documents associated with their inpatient treatment including the respective discharge letters were saved in their digital medical file. Laboratory results, such as serum ethanol/phosphatidylethanol, ethyl glucuronide, and carbohydrate-deficient transferrin, acquired during the observation period were accessible through the digital medical file. However, these biomarkers were not routinely assessed and hence not comprehensively available.

Using the above-mentioned individual documentation, each patient's AU behavior after TIPS implantation/HVPG measurement was carefully assessed in a dichotomic way (AU/no AU). Patients in whom one or more AU episodes after TIPS implantation/HVPG measurement were documented were placed in the AU group, while those in whom alcohol abstinence was exclusively documented throughout the entire observation period were placed in the non-AU group for further analyses.

To support the acquired data on AU, all inpatient discharge reports issued after the date of TIPS implantation were assessed for alcohol-related admission diagnoses such as “alcohol intoxication”, “alcohol-related steatohepatitis”, “alcohol-related pancreatitis”, etc. Furthermore, to provide longitudinal objective supporting information regarding AU, we recorded mean corpuscular hemoglobin volume (MCV) and gamma-glutamyl transpeptidase (GGT) levels at baseline (BL; defined as the date of TIPS implantation) as well as 6 months, 12 months, 24 months, and 36 months after TIPS implantation, respectively [25].

2.5 | TIPS Procedure

The implantation of self-expandable polytetrafluorethylene-covered TIPS was performed according to standard operating procedures as previously specified [2, 26–28]. During the TIPS procedure, the portosystemic pressure gradient (PPG; defined as the difference between right atrial pressure and directly measured portal venous pressure prior to TIPS placement) was recorded by the performing radiologist [28]. Routine surveillance after TIPS implantation included clinical and laboratory follow-up every 3 after the procedure [28].

2.6 | Statistics

Microsoft Excel for Mac (Version 16.77.1, 2023) was used for data management. Statistical analyses and generation of figures and tables were performed using IBM SPSS Statistics (Version 29.0.0.0, 2022), R by R Foundation for Statistical Computing (Version R 4.3.2, 2023), and GraphPad Prism (Prism 10 for macOS, Version 10.2.2, 2024).

Categorical variables were reported as number (n) and proportion (%) of patients with the characteristic of interest. Continuous variables were described using median and interquartile range (IQR). Group comparisons of categorical variables were performed using Pearson's Chi-squared test or Fisher's exact test as appropriate. The Mann–Whitney U test and the Kruskal–Wallis test were applied for the comparison of continuous variables between two and three or more groups, respectively. Spearman's rho was used for the assessment of correlations. Linear regression analysis was performed to identify factors and outcome parameters associated with AU. Clinical outcomes were investigated by calculation of cumulative incidence. Gray's test was implemented for cumulative incidence comparison. Competing risk regression models using the R package cmprsk were applied for the assessment of an association between AU and the occurrence of the clinical outcomes of interest [29]. Aside from AU, sex as well as established factors associated with worse outcomes in ACLD were investigated by univariate and multivariate analyses. OLT and non-liver-related death were defined as competing risks in cumulative incidence comparisons and competing risk regression analyses. Characteristics that were associated with the parameter of interest in univariate analysis ($p < 0.100$) were included in the multivariate model in linear regression models as well as competing risk regression models.

2.7 | Ethics Statement

The study protocol was conceptualized in accordance with the ethical principles stated in the 1975 Declaration of Helsinki and approved by the ethics committees of the Medical University of

Vienna (EK 1760/2014, EK 1943/2017) and of the City of Vienna (MA15, 14-264-VK).

3 | Results

3.1 | Study Population

Overall, 276 patients with ALD-associated ACLD underwent TIPS implantation in the participating centers between 2000 and 2022 (Figure 1). After exclusion of 28 individuals with a follow-up period < 90 days after TIPS placement, a total of 248 patients were included in the study (Figure 1, Figure S1).

3.2 | Characteristics of Patients Undergoing TIPS Implantation

The study population was predominantly male (78.2%) with a median age of 55.5 (50.0; 62.0) years (Table 1). Twenty (8.1%) ALD patients had viral hepatitis as an additional etiological factor contributing to ACLD. Recurrent and/or refractory ascites was the main indication for TIPS implantation in 173 (69.8%) individuals. Most patients were classified as CP B at BL (145/195, 74.4%) and the median MELD score was 12.0 (9.2; 17.0). Through TIPS placement, the median PPG was reduced from 20.0 (16.0; 24.0) mmHg to 7.00 (5.0; 10.0) mmHg.

3.3 | Comparison of Baseline Characteristics According to Alcohol Use Patterns in Patients Undergoing TIPS Implantation

Among our study cohort, ongoing AU after TIPS implantation was documented in 90 (36.3%) individuals, while in 158 (63.7%) post TIPS alcohol abstinence was recorded (Figure 1, Table 1). Throughout the observation period of 36 months, GGT and MCV were significantly higher among those who continued to use alcohol after TIPS implantation (Figure S2).

Most of the BL characteristics were comparable between the two groups; however, patients with ongoing AU were significantly younger (54.0 [47.2, 58.8] vs. 57.5 [51.0; 64.0] years, $p < 0.001$) and showed higher BL GGT levels (126 [76; 214] vs. 102 [57; 172] U/L, $p = 0.036$) than those without post TIPS AU. Of note, cigarette smoking was more common among the AU cohort as compared to those with post TIPS alcohol abstinence (currently smoking at BL: 67.5% vs. 44.9%; never smoked: 20.5% vs. 29.3%; $p = 0.003$).

3.4 | Follow-Up and Clinical Outcomes of Patients Undergoing TIPS Implantation

During a median follow-up (FU) of 30 (8; 62) months, 164 (66.1%) patients experienced at least one further decompensation event (variceal bleeding in 18 [7.3%], ascites in 79 [31.9%], and HE in 120 [48.4%] participants) (Table 2). Bacterial infections occurred in 92 (37.1%) individuals, 11 (12.0%) of which were attributed to SBP. A total of 96 (38.7%) patients were admitted with ACLF. HCC was diagnosed in 22 (8.9%) patients during FU, while 24 (15.2%) patients who remained abstinent from alcohol after TIPS underwent OLT. Overall, 151 (60.9%) patients died within the FU period, 103 (68.2%) of whom had liver-related causes of death.

3.5 | Comparison of Outcomes According to Alcohol Use Patterns in Patients Undergoing TIPS Implantation

Patients with ongoing AU were followed for a median of 37.5 (18.0; 65.0) months, while those without post TIPS AU had a slightly lower median FU of 32.5 (9.3; 67.0) months ($p = 0.263$). There was no difference between the two groups regarding the development of further decompensation and HCC (Table 2). However, bacterial infections were significantly more frequent among those with ongoing AU (48.9% vs. 30.4%, $p = 0.006$). Importantly, the incidence of ACLF (55.6% vs. 29.1%, $p < 0.001$), all-cause mortality (72.2% vs. 54.4%, $p = 0.009$), and liver-related

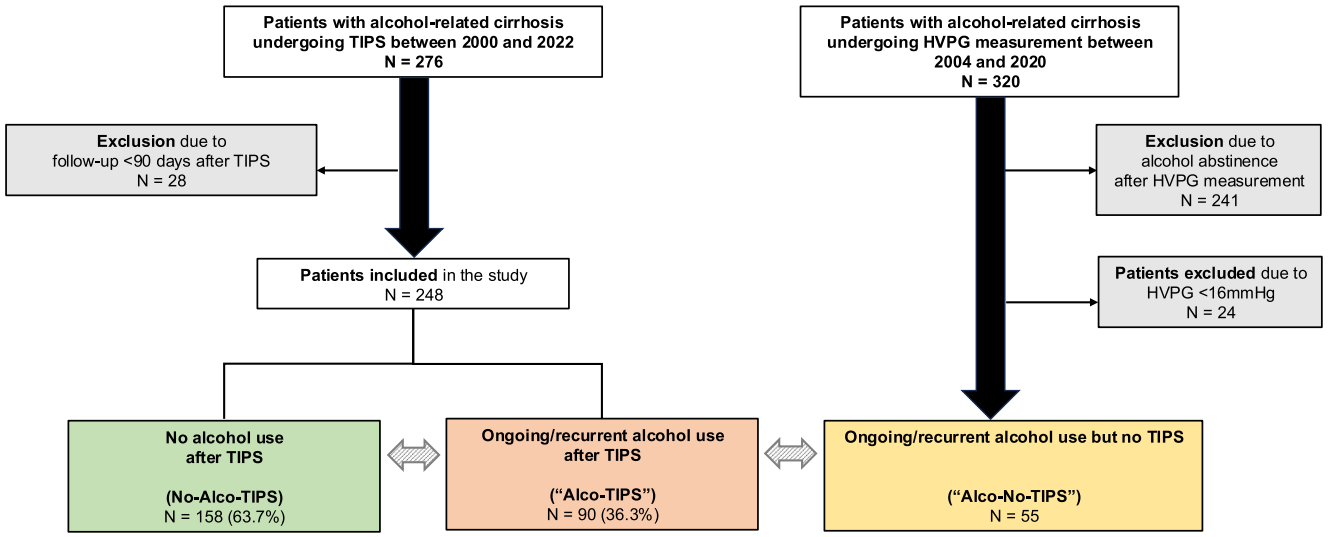

FIGURE 1 | Flowchart of the study population. HVPG, hepatovenous pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

TABLE 1 | Patient characteristics according to alcohol use after TIPS.

Variable *n* (%)	Overall 248 (100)	Abstinence after TIPS 158 (63.7)	Ongoing AU after TIPS 90 (36.3)	*p* value
Sex (*n*, [%])				0.543
Male	194 (78.2)	126 (79.8)	68 (75.6)	
Female	54 (21.8)	32 (20.3)	22 (24.4)	
Age (years), (median, [IQR])	55.5 (50.0; 62.0)	57.5 (51.0; 64.0)	54.0 (47.2; 58.8)	< 0.001
Viral hepatitis (*n*, [%])	20 (8.1)	11 (7.0)	9 (10.0)	0.547
Diabetes[a] (*n*, [%])	51 (21.9)	37 (24.7)	14 (16.9)	0.225
TIPS indication (*n*, [%])				0.071
Ascites	173 (69.8)	117 (74.1)	56 (62.2)	
Variceal bleeding	75 (30.2)	41 (26–0)	34 (37.8)	
PPG before TIPS[b] (mmHg), (median, [IQR])	20.0 (16.0; 24.0)	19.0 (16.0; 23.0)	20.0 (15.0; 24.0)	0.943
PPG after TIPS[c] (mmHg), (median, [IQR])	7.0 (5.0; 10.0)	7.0 (5.0; 9.5)	7.0 (6.0; 9.8)	0.991
Child-pugh stage C (*n*, [%])	29 (14.9)	17 (13.08)	12 (18.5)	0.319
Child-pugh score (median, [IQR])	8.0 (8.0; 9.0)	8.0 (8.0; 9.0)	8.0 (8.0; 9.0)	0.937
MELD score (points), (median, [IQR])	12.0 (9.2; 17.0)	13.0 (9.0; 18.0)	10.9 (9.9; 15.0)	0.530
Pre-TIPS history of hepatic encephalopathy[d] (*n*, [%])	50 (22.5)	33 (23.1)	17 (21.5)	0.820
Creatinine[e] (mg/dL), (median, [IQR])	1.0 (0.8; 1.3)	1.1 (0.8; 1.4)	0.9 (0.7; 1.2)	0.001
Albumin[f] (g/L), (median, [IQR])	32.6 (29.2; 36.4)	33.0 (29.8; 36.8)	32.0 (27.9; 35.7)	0.194
INR[g] (median, [IQR])	1.3 (1.1; 1.4)	1.3 (1.1; 1.4)	1.3 (1.2; 1.4)	0.491
Bilirubin[g] (mg/dL), (median, [IQR])	1.1 (0.7; 1.7)	1.1 (0.7; 1.8)	1.2 (1.0; 1.7)	0.106
GGT[g] (U/L), (median, [IQR])	108 (62.3; 195.0)	102 (57.0; 172.0)	126 (76.0; 214.0)	0.036
MCV[c] (fL), (median, [IQR])	89.9 (83.5; 95.6)	89.5 (83.2; 94.4)	91.1 (83.7; 96.2)	0.171
Sodium[h] (mmol/L), (median, [IQR])	135 (132; 138)	135 (132; 137)	135 (133; 138)	0.205
WBC[i] (G/L), (median, [IQR])	6.2 (4.5; 7.9)	6.0 (4.5; 7.5)	6.6 (4.6; 8.5)	0.164
CRP[j] (mg/dL), (median, [IQR])	1.1 (0.5; 2.2)	1.2 (0.5; 2.1)	1.0 (0.5; 2.6)	0.864

Note: The baseline of the observation period was defined as the date of TIPS implantation.
Abbreviations: CRP, C-reactive protein; GGT, gamma-glutamyl transferase; INR, international normalized ratio; MCV, mean corpuscular volume; MELD, Model of End-stage Liver Disease; PPG, portal pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt; WBC, white blood cell count.
[a]available in 233 patients.
[b]available in 220 patients.
[c]available in 221 patients.
[d]available in 222 patients.
[e]available in 227 patients.
[f]available in 205 patients.
[g]available in 218 patients.
[h]available in 228 patients.
[i]available in 229 patients.
[j]available in 219 patients.

death (53.3% vs. 34.8%, $p = 0.007$) were significantly increased among the cohort with post TIPS AU as compared to those who remained abstinent during FU.

3.6 | Impact of Ongoing Alcohol Use on Clinical Outcomes in Patients Undergoing TIPS Implantation

Patients with ongoing AU after TIPS implantation showed a higher cumulative incidence of ACLF ($p < 0.001$) as well as liver-related death ($p = 0.049$) compared to those who remained abstinent from alcohol (Figure 2). The impact of ongoing AU on the risk of ACLF and liver-related death is shown in Table 3. After adjustment for age, sex, MELD score, TIPS indication, and CRP at BL as relevant cofactors according to univariate analyses, ongoing AU was independently associated with an increased risk for the development of ACLF (adjusted subdistribution hazard ratio [asHR] 2.27; 95% CI 1.40–3.66; $p < 0.001$) and liver-related death (asHR 1.68; 95% CI 1.05–2.67; $p = 0.030$) according to multivariate competing risk regression analysis (Table 3).

In subgroup analyses stratified by TIPS indication, the higher cumulative incidence of ACLF in patients with post TIPS AU

TABLE 2 | Clinical outcomes according to alcohol use patterns.

Variable *n* (%)	Overall 248 (100)	Abstinence after TIPS 158 (63.7)	Ongoing AU after TIPS 90 (36.3)	*p* value
Any decompensation (*n*, [%])	164 (66.1)	101 (63.9)	63 (70.0)	0.405
Ascites	79 (31.9)	47 (29.8)	32 (35.6)	0.422
Variceal bleeding	18 (7.3)	10 (6.3)	8 (8.9)	0.622
Hepatic encephalopathy	120 (48.4)	76 (48.1)	44 (48.9)	1.000
Bacterial infection (*n*, [%])	92 (37.1)	48 (30.4)	44 (48.9)	0.006
SBP	11 (4.4)	9 (5.7)	2 (2.2)	0.337
ACLF (*n*, [%])	96 (38.7)	46 (29.1)	50 (55.6)	< 0.001
HCC (*n*, [%])	22 (8.9)	15 (9.5)	7 (7.8)	0.822
Death (*n*, [%])	151 (60.9)	86 (54.4)	65 (72.2)	0.009
Liver-related death	103 (41.5)	55 (34.8)	48 (53.3)	0.007
Non liver-related death	48 (19.4)	31 (19.6)	17 (18.9)	1.000

Abbreviations: ACLF, acute-on-chronic liver failure; HCC, hepatocellular carcinoma; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.

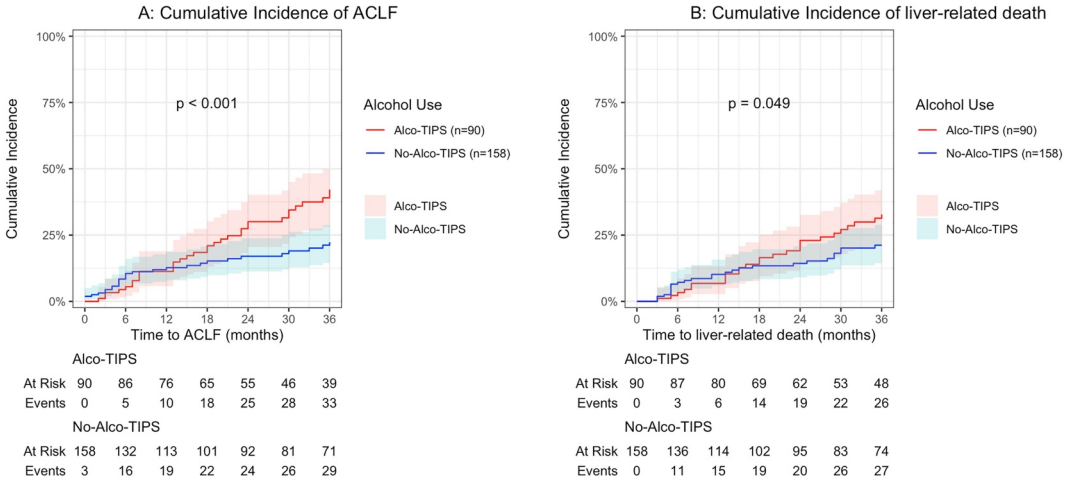

FIGURE 2 | Cumulative incidence of outcomes stratified by alcohol use patterns. Liver transplantation and non-liver-related death were determined as competing risks. Cumulative incidences were compared using Gray's test. (A) Cumulative incidence of ACLF. ACLF, acute-on-chronic liver failure; TIPS, transjugular intrahepatic portosystemic shunt. (B) Cumulative incidence of liver-related death.

(ascites as primary indication for TIPS: $p = 0.008$; variceal bleeding as primary indication for TIPS: $p = 0.013$) was retained (Figure S3 and S4). Separate multivariable competing risk regression analyses according to TIPS indication (Supporting Information S1: Tables 1 and 2) also maintained post-TIPS AU as an independent risk factor for ACLF (ascites as primary indication for TIPS: asHR 1.89; 95% CI 1.10–3.26, $p = 0.021$; variceal bleeding as primary indication for TIPS: asHR 3.93; 95% CI 1.61–9.61, $p = 0.003$). In patients receiving TIPS for variceal bleeding, ongoing AU was also shown to be a significant risk factor for liver-related death after adjusting for relevant confounding factors in the multivariable model (asHR 4.00; 95% CI 1.73–9.22, $p = 0.001$).

3.7 | Comparison to Non-Abstinent ALD Cirrhosis Patients Without TIPS (Figure 1; Table 4)

Outcomes of the subgroup of patients with ongoing AU post TIPS ($n = 90$, "Alco-TIPS") were compared to a cohort of individuals with ALD-related cirrhosis and ongoing AU without TIPS ($n = 55$; "Alco-No-TIPS") (Figure 1; Table 4).

While the demographic parameters were comparable between the two groups, patients in the "Alco-No-TIPS" group presented with overall more compromised hepatological status characterized by slightly higher MELD (12.0 [11.0; 15.0] vs. 10.9 [9.9; 15.0], $p = 0.249$), higher INR (1.4 [1.2; 1.5] vs. 1.3 [1.2; 1.4], $p = 0.009$), higher bilirubin (1.8 [1.1; 2.5] vs. 1.2 [1.0; 1.7] mg/dL, $p = 0.002$), and increased frequency of HE (41.8% vs. 21.5%, $p = 0.012$).

Median FU was balanced between the "Alco-TIPS" cohort (37.5 [18.0; 65.0] months) and the "Alco-No-TIPS" cohort (32.0 [14.0; 52.5] months, $p = 0.160$). While the incidence of further decompensation by development of recurrent ascites (35.6% vs. 54.5%, $p = 0.038$) including SBP (2.2% vs. 16.4%, $p = 0.003$) and variceal bleeding (8.9% vs. 23.6%, $p = 0.27$) was naturally higher among patients who did not undergo TIPS, most other clinical outcomes including overall mortality (72.2% vs. 72.7%,

TABLE 3 | Impact of ongoing alcohol use on the risk for (i) ACLF and (ii) liver-related death according to alcohol use patterns.

	Univariate (unadjusted) analysis			Multivariate (adjusted) analysis		
Parameter	**sHR**	**95% CI**	***p* value**	**asHR**	**95% CI**	***p* value**
(i) Outcome: ACLF						
Ongoing AU (vs. Abstinence)	2.13	1.43–3.17	**< 0.001**	2.27	1.40–3.66	**< 0.001**
Sex (M vs. F)	0.90	0.58–1.40	0.630	0.92	0.55–1.52	0.730
Age (per year)	1.00	0.98–1.02	0.950	1.01	0.99–1.03	0.400
MELD at TIPS (per point)	1.01	0.97–1.06	0.520	1.02	0.98–1.07	0.300
PPG after TIPS (per mmHg)	0.99	0.94–1.06	0.870	0.99	0.92–1.07	0.820
TIPS indication: Bleeding (vs. Ascites)	0.77	0.49–1.20	0.250	0.70	0.39–1.24	0.220
Smoking (vs. Non-smoking)	1.07	0.87–1.31	0.530	—	—	—
CRP (per mg/L)	1.02	0.91–1.14	0.760	—	—	—
(ii) Outcome: Liver-related death						
Ongoing AU (vs. Abstinence)	1.65	1.13–2.42	**0.010**	1.68	1.05–2.67	**0.030**
Sex (M vs. F)	0.88	0.56–1.38	0.580	0.81	0.47–1.40	0.450
Age (per year)	1.02	1.00–1–04	0.075	1.02	1.00–1.05	0.084
MELD at TIPS (per point)	1.02	0.98–1.06	0.300	1.02	0.97–1.06	0.500
PPG after TIPS (per mmHg)	1.03	0.98–1.09	0.210	1.06	0.99–1.13	0.100
TIPS indication: Bleeding (vs. Ascites)	0.70	0.46–1.08	0.110	0.68	0.38–1.20	0.180
Smoking (vs. Non-smoking)	1.04	0.85–1.26	0.730	—	—	—
CRP (per mg/L)	1.12	1.02–1.23	**0.015**	1.10	0.99–1.22	0.093

Note: Univariate and multivariate Fine and Gray competing risk regression models are shown. Liver transplantation and non-liver-related death were determined as competing risks. *p* values in bold indicate statistical significance.
Abbreviations: ACLF, acute-on-chronic liver failure; asHR, adjusted sHR; AU, alcohol use; CRP, C-reactive protein at baseline; MELD, Model of End-stage Liver Disease; PPG, portal pressure gradient; sHR, subdistribution hazard ratio; TIPS, transjugular intrahepatic portosystemic shunt.

$p = 1.000$) as well as liver-related mortality (53.3% vs. 60.0%, $p = 0.540$) and ACLF (55.6% vs. 63.5%, $p = 0.457$) were comparable between the "Alco-TIPS" and the "Alco-No-TIPS" cohort (Table 4).

ALD patients with ongoing AU who underwent TIPS implantation showed a comparable cumulative incidence of ACLF as those who were managed without TIPS ($p = 0.357$, Figure 3A). Furthermore, there was no difference regarding the cumulative incidence of liver-related death between those managed with versus without TIPS ($p = 0.073$, Figure 3B).

Competing risk regression analyses were performed to investigate the impact of TIPS implantation on the risk of ACLF and liver-related death in patients with ongoing AU during FU (Table 5). After adjustment for age, sex, MELD score, and CRP at baseline, TIPS implantation did not show a significant association with increased risk for the development of ACLF (asHR 0.70; 95% CI 0.45–1.10; $p = 0.120$) or liver-related death (asHR 0.66; 95% CI 0.41–1.07; $p = 0.094$).

4 | Discussion

TIPS implantation represents the recommended treatment for severe complications of PH as it prevents mortality and may allow successful bridging to OLT [2, 9, 10, 16]. In a subgroup of patients with decompensated dACLD, PH complications may even be sustainably resolved after TIPS placement [15]; especially in patients who are not eligible for OLT, TIPS may serve as a definite treatment [10, 18, 27].

AU disorder is associated with significant morbidity and mortality and represents one of the leading causes of liver cirrhosis in the Western world [30]. Ongoing AU currently remains an exclusion criterion for OLT in patients with ALD as graft survival and clinical outcomes are detrimental in patients in whom post-OLT abstinence cannot be achieved [19, 21, 31]. However, patients with ALD-associated dACLD and ongoing AU may undergo TIPS implantation as a (definite) treatment option. While the clinical benefits of TIPS implantation for PH due to ALD cirrhosis have been demonstrated in numerous studies, data on the frequency and impact of post-TIPS AU currently remain scarce [10, 12, 13, 26, 27].

A retrospective data analysis of 199 patients who received TIPS for ALD-associated dACLD in the USA showed an alcohol recidivism rate of 5.5% at one month, 10.1% at 3 months, and 22.1% at 6–12 months [22], which was slightly below the post-TIPS AU rate of 36.3% observed in our study population. However, our findings are consistent with post-OLT scenarios where ongoing AU was reported in 10%–50% [21, 31]. Importantly, we found a significantly higher percentage of tobacco use among patients with ongoing AU as compared to those who achieved post-TIPS alcohol abstinence in our study cohort (67.5% vs. 44.9%, $p = 0.003$), which goes in line with the available literature demonstrating that the co-prevalence of other

TABLE 4 | Comparison of non-abstinent cirrhosis patients managed with versus without TIPS.

Variable *n* (%)	"Alco-TIPS" 90	"Alco-No-TIPS" 55	*p* value
Sex (*n*, [%])			0.678
Male	68 (75.6)	44 (80.0)	
Female	22 (24.4)	11 (20.0)	
Age (years), (median, [IQR])	54.0 (47.2; 58.8)	54.0 (48.0; 59.0)	0.518
PPG pre-TIPS/HVPG at BL[a] (mmHg), (median, [IQR])	20.0 (15.0; 24.0)	21.0 (19.0; 24.0)	0.017
Child-pugh stage C (*n*, [%])	12 (18.2)	11 (20.0)	0.432
Child-pugh score (median, [IQR])	8.0 (8.0; 9.0)	7.0 (7.0; 9.0)	0.061
MELD score (points), (median, [IQR])	10.9 (9.9; 15.0)	12.0 (11.0; 15.0)	0.249
Previous decompensation events (*n*, [%])			
Hepatic Encephalopathyb	17 (21.5)	23 (41.8)	0.012
Variceal Bleeding	29 (32.2)	21 (38.2)	0.581
Ascites	65 (72.2)	49 (89.1)	0.028
BL creatinine[b] (mg/dL), (median, [IQR])	0.9 (0.7; 1.2)	0.8 (0.7; 1.1)	0.145
BL albumin[c] (g/L), (median, [IQR])	32.0 (27.9; 35.7)	34.2 (30.6; 37.5)	0.077
BL INR[d] (median, [IQR])	1.3 (1.2; 1.4)	1.4 (1.2; 1.5)	0.009
BL bilirubin[e] (mg/dL), (median, [IQR])	1.2 (1.0; 1.7)	1.8 (1.1; 2.5)	0.002
BL GGT (U/l), (median, [IQR])	126 (76; 214)	145 (95; 334)	0.152
BL sodium[e] (mmol/L), (median, [IQR])	135 (133; 138)	136 (133; 139)	0.755
BL WBC[e] (G/L), (median, [IQR])	6.6 (4.6; 8.5)	5.8 (4.6; 7.7)	0.186
BL CRP[f] (mg/dL), (median, [IQR])	1.0 (0.5; 2.6)	0.6 (0.3; 1.1)	0.007
Follow-up			
Follow-up time (months), (median, [IQR])	37.5 (18.0; 65.0)	32.0 (14.0; 52.5)	0.160
Any further decompensation (*n*, [%])	63 (70.0)	43 (78.2)	0.376
Recurrent Ascites	32 (35.6)	30 (54.5)	0.038
Variceal Bleeding	8 (8.9)	13 (23.6)	0.027
Hepatic Encephalopathy	44 (48.9)	21 (38.2)	0.278
SBP (*n*, [%])	2 (2.2)	9 (16.4)	0.003
ACLF[g] (*n*, [%])	50 (55.6)	33 (63.5)	0.457
HCC (*n*, [%])	7 (7.8)	3 (5.5)	0.742
Death (*n*, [%])	65 (72.2)	40 (72.7)	1.000
Liver-Related death	48 (53.3)	33 (60.0)	0.540
Non Liver-related death	17 (18.9)	8 (14.5)	0.656

Note: The comparison cohort ("Alco-No-TIPS") consisted of patients with ALD-related decompensated cirrhosis with an HVPG ≥ 16mmHg who had a history of either ascites and/or variceal bleeding and who did not undergo TIPS implantation. The baseline of the observation period was defined as the date of TIPS implantation in patients undergoing TIPS and the date of the first HVPG measurement in patients not undergoing TIPS, respectively. In patients who underwent TIPS, PPG before TIPS implantation was reported while in patients not undergoing TIPS, HVPG at the first HVPG measurement was reported.

Abbreviations: ACLF, acute-on-chronic liver failure; ALD, alcohol-related liver disease; BL, baseline; CRP, C-reactive protein; HCC, hepatocellular carcinoma; HVPG, hepatovenous pressure gradient; INR, international normalized ratio; MELD, Model of End-stage Liver Disease; PPG, portal pressure gradient; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt; WBC, white blood cell count.

[a]available in 137 patients.
[b]available in 134 patients.
[c]available in 124 patients.
[d]available in 132 patients.
[e]available in 135 patients.
[f]available in 130 patients.
[g]available in 52 patients who did not undergo TIPS.

substance use disorders and/or psychiatric comorbidities may predispose for alcohol recidivism among patients with ALD [22, 32]. This emphasizes the need to not only focus on and treat AU disorder but to also screen for other substance use disorders and consider them in potential therapeutic concepts among patients with ALD [30, 33].

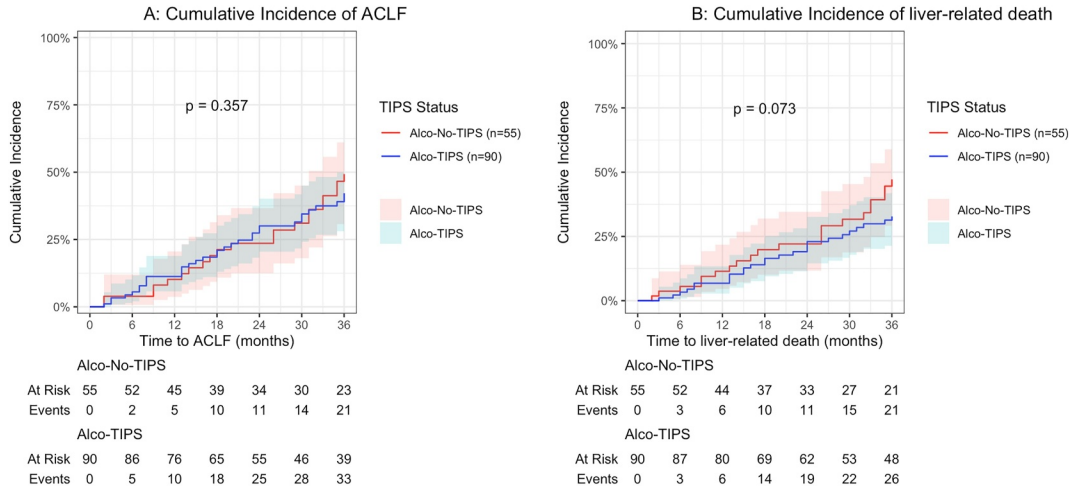

FIGURE 3 | Cumulative incidence of outcomes stratified by management with or without TIPS. Liver transplantation and non-liver-related death were determined as competing risks. Cumulative incidences were compared using Gray's test. (A) Cumulative incidence of ACLF. ACLF, acute-on-chronic liver failure; TIPS, transjugular intrahepatic portosystemic shunt. (B) Cumulative incidence of liver-related death.

TABLE 5 | Impact of ongoing alcohol use on the risk for (i) ACLF and (ii) liver-related death according to management with or without TIPS.

	Univariate (unadjusted) analysis			Multivariate (adjusted) analysis		
Parameter	**sHR**	**95% CI**	***p* value**	**asHR**	**95% CI**	***p* value**
(i) Outcome: ACLF						
TIPS placement (vs. No TIPS)	0.75	0.49–1.14	0.180	0.70	0.45–1.10	0.120
Sex (M vs. F)	0.65	0.42–1.00	0.052	0.62	0.39–1.00	0.052
Age (per year)	1.00	0.97–1.02	0.550	0.99	0.97–1.01	0.360
MELD at TIPS/HVPG (per point)	1.07	1.01–1.13	**0.030**	1.07	1.01–1.13	**0.033**
Smoking (vs. Non-smoking)	1.20	0.87–1.65	0.270	—	—	—
CRP (per mg/L)	1.00	0.93–1.08	0.970	—	—	—
(ii) Outcome: Liver-related death						
TIPS placement (vs. No TIPS)	0.73	0.47–1.14	0.170	0.66	0.41–1.07	0.094
Sex (M vs. F)	0.57	0.35–0.92	**0.021**	0.61	0.35–1.08	0.090
Age (per year)	1.00	0.97–1.02	0.810	1.00	0.97–1.02	0.820
MELD at TIPS/HVPG (per point)	1.05	1.00–1.11	0.055	1.05	0.98–1.12	0.200
Smoking (vs. Non-smoking)	1.38	0.98–1.95	0.064	—	—	—
CRP (per mg/L)	1.07	1.01–1.13	**0.018**	1.06	1.00–1.13	**0.041**

Note: The comparison cohort ("Alco-no-TIPS") consisted of patients with ALD-related decompensated cirrhosis with an HVPG ≥ 16mmHg who had a history of either ascites and/or variceal bleeding and who did not undergo TIPS implantation. The baseline of the observation period was defined as the date of TIPS implantation in patients undergoing TIPS and the date of the first HVPG measurement in patients not undergoing TIPS, respectively. Univariate and multivariate Fine and Gray competing risk regression models are shown. Liver transplantation and non-liver-related death were determined as competing risks. *p* values in bold indicate statistical significance.

Abbreviations: ACLF, acute-on-chronic liver failure; asHR, adjusted sHR; CRP, C-reactive protein at baseline; HVPG, hepatovenous pressure gradient; MELD, Model of End-stage Liver Disease; sHR, subdistribution hazard ratio; TIPS, transjugular intrahepatic portosystemic shunt.

Our data showed a substantial increase in ACLF-incidence among patients with ongoing AU after TIPS in the overall as well as in subgroup analyses stratified by TIPS indication. Of note, the detrimental impact of post-TIPS AU was maintained in multivariable competing risks regression models, identifying post-TIPS AU as an independent risk factor for a deterioration in outcomes. Ongoing AU remained an independent risk factor for the development of ACLF in multivariable competing risks analyses stratified by TIPS indication, and predisposed patients undergoing TIPS for ascites toward liver-related death despite falling just below the level of significance (asHR 1.64, 95% CI 0.98–2.74; $p = 0.058$). Moreover, ongoing AU was independently associated with liver-related death in patients undergoing TIPS for variceal bleeding; it became significant (asHR 4.00, 95% CI 1.73–9.22; $p = 0.001$). By performing these subgroup analyses stratified by TIPS indication, we aimed to explore whether the association between post-TIPS AU and adverse outcomes differed by TIPS indication; however, while the respective

results support our findings, it has to be taken into consideration that the resulting subgroups were small and validation in larger cohorts is needed.

Cumulative incidence visualization regarding ACLF and liver-related death revealed overlapping confidence intervals and a separation of curves, demonstrating a discrimination concerning risk toward the respective outcomes, approximately 2 years from BL (Figure 2 and 3). Because of the exploratory design of this study, our interpretation remains speculative, yet it seems likely that a combination of factors contributes to this phenomenon. First, the risk for ALD-associated complications all included patients shared due to the decompensated liver disease and hazardous AU that were universally prevalent at BL, which was only modified by abstinence or ongoing AU over time. Second, the initial HVPG reduction achieved through TIPS followed by the individual reestablishment of risk behavior through AU post-TIPS. Ultimately, modifying factors aside from AU that were not specifically assessed in this study, such as nutrition, physical activity, and psychological wellbeing, may contribute substantially to individual outcomes over time.

While our observation period of a median 32.0 ("Alco-No-TIPS") and 37.5 ("Alco-TIPS") years did not reveal any difference in ACLF or mortality among the two groups, the incidence of recurrent ascites, SBP, and variceal bleeding was significantly reduced in the "Alco-TIPS" cohort, suggesting that TIPS may still improve clinical outcomes among patients with ongoing AU (Table 4). As our study cohorts were limited in size and FU periods varied grossly among the included patients, a relevant effect of ongoing AU and/or TIPS on mortality may have been overlooked by our specific analyses. Therefore, further investigation in larger prospective studies is necessary to validate our findings and to refine recommendations for TIPS implantation in patients with ALD-related dACLD and ongoing AU.

Despite the clinical relevance of our findings, our study has some limitations. First and foremost, it must be acknowledged that AU was assessed by structured patient interviews, physician recordings, and indirect blood-based biomarkers; therefore, we solely based our analysis on a binary assessment of AU without further quantification or longitudinal assessment of alcohol intake, which represents the main weakness of our study. This retrospective assessment of AU, including potential underreporting, represents potential bias and is the main limitation of our study. While our approach to AU assessment does not allow for discrimination between no versus different extents of AU and its effects on post-TIPS outcomes, all patients analyzed in the AU group did have documented AU during the observation period; however, it cannot be reliably ruled out that patients in the non-AU group may have had occasional or moderate unreported/undetected AU. In future prospective studies, post-TIPS AU should be objectively investigated by using validated questionnaires (e.g., AUDIT) in combination with direct alcohol biomarkers. However, indirect alcohol-related surrogates, that is GGT and MCV levels [25], were available and were significantly higher in ALD patients with post-TIPS AU, supporting the value of our binary assessment of post-TIPS AU (Supporting Information S2: Figure S2). Secondly, no prospective study protocol was followed due to the retrospective design of the study, and psychiatric comorbidities could not be assessed in a systematic way. Related to the long observation period spanning up to 25 years, changes in standards for the management of PH, specifically HE, over time may result in the potential heterogenicity of our study cohort. However, post-TIPS AU is a constant and ongoing phenomenon with the potential to affect any patient undergoing TIPS for ALD-related complications of cirrhosis independent of the respective treatment period, while national guidelines [2] for PH management have been in place and regularly updated, thereby supporting consistent and comprehensible management according to the respective time periods within our study population. Furthermore, the comparison cohort with ongoing AU who did not receive TIPS was smaller than the subgroup undergoing TIPS and reasons why TIPS was not performed in this subgroup were not systematically retrieved. While we believe it is a positive signal that a large share of ALD patients with decompensated cirrhosis can be treated with TIPS, absolute and relative contraindications [2] must be carefully assessed before indicating the intervention. At our center, this evaluation is made based on current guidelines [2] upon interdisciplinary discussion in regularly performed dedicated TIPS board sessions. Due to the retrospective nature of the analyses performed in this study, potential indications for TIPS and consecutive reasoning why TIPS was eventually abandoned in the no-TIPS group were not available as, according to clinical protocols at the participating centers, only patients considered eligible for TIPS are discussed in the interdisciplinary TIPS boards, for which corresponding written protocols including the final verdict pro or contra TIPS implantation and specific respective reasoning are provided. It is likely that in the no-TIPS group, contraindications according to current guidelines, limited performance status, and/or lack of patients' consent led to refraining from discussion in the respective interdisciplinary TIPS board and, hence, only clinical documentation, which was not comprehensively accessible for the study team, but not the official TIPS board's protocol were available in most of these patients. Ultimately, there may be a selection bias due to the exclusion of patients who died within 90 days after TIPS placement. The selection of this minimum follow-up of 90 days was made based on clinical observations with the idea to rule out—as well as possible, given the study design—the influence of acute events, e.g. infections or excessive AU prior to TIPS, at the time of TIPS implantation, and acute or short-term procedure-related complications [34, 35] as the cause of negative short-term post-TIPS outcomes. Additionally, we aimed to ensure that all patients were discharged from the hospital and had time to reestablish potential AU patterns to obtain results as reliable as possible according to the study design. To our knowledge, there is currently no data supporting a specific minimum post-TIPS follow-up time with regard to our study objective; hence, the cutoff of 90 days post-TIPS implantation was chosen for this analysis. Importantly, among the 28 patients who were excluded due to insufficient FU time, 18 (64.3%) died within 90 days after TIPS, yet only 3/18 (16.7%) ongoing AU was documented. One of these three patients died due to interventional complications during the TIPS procedure while for the remaining two the cause of death could not be retrieved from the available data. Additionally, it must be considered that our study cohort was derived from two tertiary care centers and may therefore differ from patient cohorts treated in peripheral settings, underlining the need for external validation through future studies.

Considering the clinical implications of our findings and the high prevalence of ongoing AU among patients undergoing TIPS for ALD, we believe that the results of our study add important data to improve post-TIPS optimization in patients with ALD. Most importantly, our data may support the specification of patients with ALD-related cirrhosis benefiting from TIPS implantation, as compared to those in whom TIPS may not lead to any clinical improvement or could even be associated with increased liver-related complications [2].

Achieving alcohol abstinence in patients with ALD is challenging, and once accomplished, its maintenance requires a lifelong effort from patients and their caregivers, including health care workers and physicians [30, 33]. The results from our study highlight the paramount role of close multidisciplinary collaboration to facilitate long-term success of hepatological treatment in ALD cirrhosis patients and promote harm reduction measures to support alcohol abstinence whenever possible. Our findings may add to guiding the design of multidisciplinary post-TIPS support programs which should focus on psychiatric assistance in strong conjunction with dietological measures, physical activity, and social reintegration plans to facilitate alcohol abstinence and improve overall outcomes in patients undergoing TIPS for ALD-related complications.

Author Contributions

Caroline Schwarz: conceptualization, investigation, writing – original draft, formal analysis, data curation. **Andrea Kornfehl:** data curation. **Reema Abid:** data curation. **Theresa Muellner-Bucsics:** writing – review and editing, data curation, supervision. **Julia Kappel:** data curation. **Michael Schwarz:** formal analysis, visualization. **Benedikt Hofer S:** data curation, writing – review and editing. **Nina Dominik:** data curation, writing – review and editing. **Georg Kramer:** data curation, writing – review and editing. **Benedikt Simbrunner:** writing – review and editing. **Mathias Jachs:** writing – review and editing. **Lukas Reider:** writing – review and editing, resources. **Michael Trauner:** writing – review and editing. **Mattias Mandorfer:** writing – review and editing, resources. **Thomas Reiberger:** writing – review and editing, conceptualization, supervision. **Lukas Hartl:** conceptualization, investigation, writing – review and editing, supervision, data curation, project administration.

Funding

The data analyzed in this study are partly derived from a prospective registry (AUTIPS) funded through the Clinical Science Award 2017 granted by the Austrian Society for Gastroenterology and Hepatology. Some authors (BSH, GK, BS, TR) were co-supported by the Austrian Federal Ministry for Digital and Economic Affairs, the National Foundation for Research, Technology and Development, the Christian Doppler Research Association, and Boehringer Ingelheim. Some authors (TM-B, JK, BSH, ND, GK, BS, MJ, MT, MM, TR, LH) were supported by the Clinical Research Group MOTION, Medical University of Vienna, Vienna, Austria—a project funded by the Clinical Research Groups Program of the Ludwig Boltzmann Gesellschaft (Grant Nr: LBG_KFG_22_32) with funds from the Fonds Zukunft Österreich.

Acknowledgement

Open Access funding provided by Medizinische Universitat Wien/KEMÖ.

Conflicts of Interest

Caroline Schwarz has received travel support from Abbvie, Gilead, Gebro, and Galápagos; speaking honoraria from Abbvie and Gilead; and payments for consulting from Gilead. Theresa Müllner-Bucsicsdid not receive any relevant grant support or honoraria within the past 5 years. Michael Schwarz has received speaking honoraria from BMS and travel support from BMS, MSD, Abbvie, and Gilead. Benedikt Simbrunner has received travel support from AbbVie, Gilead, and Falk. Mathias Jachs has served as a speaker and/or consultant for Gilead Sciences Inc. Michael Trauner has received grant support from Albireo, Alnylam, Cymabay, Falk, Genentech, Gilead, Intercept, MSD, Takeda and Ultragenyx, honoraria for consulting from Abbvie, Albireo, Agomab, Boehringer Ingelheim, BiomX, Chemomab, Falk, Genfit, Gilead, GSK, Hightide, Intercept, Ipsen, MSD, Novartis, Phenex, Pliant, Regulus, Siemens and Shire, speaker fees from Bristol-Myers Squibb, Falk, Gilead, Intercept, MSD and MAdirgal as well as travel support from AbbVie, Falk, Gilead; Jannsenand Intercept and is the co-inventor of patents on the medical use of 24-norursodesoxycholic acid. Mattias Mandorfer has served as a speaker and/or consultant and/or advisory board member for AbbVie, Bristol-Myers Squibb, Collective Acumen, Gilead, and W. L. Gore & Associates and received travel support from AbbVie, Bristol-Myers Squibb, and Gilead. Thomas Reiberger has received grant support from Abbvie, Boehringer Ingelheim, Gilead, Intercept/Advanz Pharma, MSD, Myr Pharmaceuticals, Philips Healthcare, Pliant, Siemens and W. L. Gore & Associates; speaking/writing honoraria from Abbvie, Echosens, Gilead, GSK, Intercept/Advanz Pharma, Pfizer, Roche, MSD, Siemens, W. L. Gore & Associates; consulting/advisory board fee from Abbvie, Astra Zeneca, Bayer, Boehringer Ingelheim, Gilead, Intercept/Advanz Pharma, MSD, Resolution Therapeutics, Siemens; and travel support from Abbvie, Boehringer Ingelheim, Dr. Falk Pharma, Gilead, and Roche. All other authors declare no conflicts of interest.

Data Availability Statement

Pseudonymized data, analytical methods, and study materials will be made available to other researchers upon request.

References

1. D. S. Karagiannakis, N. D. Karakousis, and T. Androutsakos, "B-Blockers in Liver Cirrhosis: A Wonder Drug for Every Stage of Portal Hypertension? A Narrative Review," *Biomedicines* 12, no. 1 (December 2023): 57, https://doi.org/10.3390/biomedicines12010057.

2. M. Mandorfer, E. Aigner, M. Cejna, et al., "Austrian Consensus on the Diagnosis and Management of Portal Hypertension in Advanced Chronic Liver Disease (Billroth IV)," supplement, *Wiener Klinische Wochenschrift* 135, no. Suppl 3 (September 2023): 493–523, https://doi.org/10.1007/s00508-023-02229-w.

3. M. Schwarz, C. Schwarz, L. Burghart, et al., "Late-Stage Presentation With Decompensated Cirrhosis is Alarmingly Common But Successful Etiologic Therapy Allows for Favorable Clinical Outcomes," *PLoS One* 18, no. 8 (2023): e0290352, https://doi.org/10.1371/journal.pone.0290352.

4. R. de Franchis, J. Bosch, G. Garcia-Tsao, et al., "Baveno VII - Renewing Consensus in Portal Hypertension," *Journal of Hepatology* 76, no. 4 (April 2022): 959–974, https://doi.org/10.1016/j.jhep.2021.12.022.

5. B. S. Hofer, B. Simbrunner, L. Hartl, et al., "Hepatic Recompensation According to Baveno VII Criteria is Linked to a Significant Survival Benefit in Decompensated alcohol-related Cirrhosis," *Liver Int Off J Int Assoc Study Liver* 43, no. 10 (October 2023): 2220–2231, https://doi.org/10.1111/liv.15676.

6. T. Reiberger and B. S. Hofer, "The Baveno VII Concept of Cirrhosis Recompensation," *Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver* 55, no. 4 (April 2023): 431–441, https://doi.org/10.1016/j.dld.2022.12.014.

7. L. Balcar, M. Tonon, G. Semmler, et al., "Risk of Further decompensation/mortality in Patients With Cirrhosis and Ascites as the First Single Decompensation Event," *JHEP Rep Innov Hepatol* 4, no. 8 (August 2022): 100513, https://doi.org/10.1016/j.jhepr.2022.100513.

8. S. G. Rodrigues, Y. P. Mendoza, and J. Bosch, "Beta-Blockers in Cirrhosis: Evidence-Based Indications and Limitations," *JHEP Rep Innov Hepatol* 2, no. 1 (February 2020): 100063, https://doi.org/10.1016/j.jhepr.2019.12.001.

9. European Association for the Study of the Liver, "European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the Management of Patients With Decompensated Cirrhosis," *Journal of Hepatology* 69, no. 2 (August 2018): 406–460, https://doi.org/10.1016/j.jhep.2018.03.024.

10. G. Iannone, E. Pompili, C. De Venuto, et al., "The Role of Transjugular Intrahepatic Portosystemic Shunt for the Management of Ascites in Patients With Decompensated Cirrhosis," *Journal of Clinical Medicine* 13, no. 5 (February 2024): 1349, https://doi.org/10.3390/jcm13051349.

11. I. M. Gralnek, D. M. Camus, J. C. Garcia-Pagan, et al., "Endoscopic Diagnosis and Management of Esophagogastric Variceal Hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline," *Endoscopy* 54, no. 11 (November 2022): 1094–1120, https://doi.org/10.1055/a-1939-4887.

12. V. Hernández-Gea, B. Procopet, Á Giráldez, et al., "Preemptive-TIPS Improves Outcome in High-Risk Variceal Bleeding: An Observational Study," *Hepatol Baltim Md* 69, no. 1 (January 2019): 282–293, https://doi.org/10.1002/hep.30182.

13. T. Bucsics, M. Schoder, N. Goeschl, et al., "Re-bleeding Rates and Survival After Early Transjugular Intrahepatic Portosystemic Shunt (TIPS) in Clinical Practice," *Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver* 49, no. 12 (December 2017): 1360–1367, https://doi.org/10.1016/j.dld.2017.08.002.

14. A. Mukund, S. Vasistha, A. Jindal, Y. Patidar, and S. K. Sarin, "Emergent Rescue Transjugular Intrahepatic Portosystemic Shunt Within 8 H Improves Survival in Patients With Refractory Variceal Bleed," *Hepatology International* 17, no. 4 (August 2023): 954–966, https://doi.org/10.1007/s12072-022-10479-5.

15. H. Larrue, G. D'Amico, P. Olivas, et al., "TIPS Prevents Further Decompensation and Improves Survival in Patients With Cirrhosis and Portal Hypertension in an Individual Patient Data Meta-Analysis," *Journal of Hepatology* 79, no. 3 (September 2023): 692–703, https://doi.org/10.1016/j.jhep.2023.04.028.

16. L. W. Unger, T. Stork, T. Bucsics, et al., "The Role of TIPS in the Management of Liver Transplant Candidates," *United Eur Gastroenterol J* 5, no. 8 (December 2017): 1100–1107, https://doi.org/10.1177/2050640617704807.

17. L. W. Unger, G. A. Berlakovich, M. Trauner, and T. Reiberger, "Management of Portal Hypertension Before and After Liver Transplantation," *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 24, no. 1 (January 2018): 112–121, https://doi.org/10.1002/lt.24830.

18. L. Büttner, A. Aigner, L. Pick, et al., "25 Years of Experience With Transjugular Intrahepatic Portosystemic Shunt (TIPS): Changes in Patient Selection and Procedural Aspects," *Insights Imaging* 13, no. 1 (April 2022): 73, https://doi.org/10.1186/s13244-022-01216-5.

19. J. Lim, M. P. Curry, and V. Sundaram, "Risk Factors and Outcomes Associated With Alcohol Relapse After Liver Transplantation," *World Journal of Hepatology* 9, no. 17 (2017): 771, https://doi.org/10.4254/wjh.v9.i17.771.

20. B. S. Hofer, B. Simbrunner, L. Hartl, et al., "Alcohol Abstinence Improves Prognosis Across all Stages of Portal Hypertension in Alcohol-Related Cirrhosis," *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc.* 21, no. 9 (August 2023): 2308–2317.e7, https://doi.org/10.1016/j.cgh.2022.11.033.

21. S. Kodali, M. Kaif, R. Tariq, and A. K. Singal, "Alcohol Relapse After Liver Transplantation for Alcoholic Cirrhosis—Impact on Liver Graft and Patient Survival: A Meta-Analysis," *Alcohol and Alcoholism* 53, no. 2 (March 2018): 166–172, https://doi.org/10.1093/alcalc/agx098.

22. I. Cam, M. Gencturk, N. Lim, et al., "Alcohol Recidivism Following Transjugular Intrahepatic Portosystemic Shunt Placement: Frequency and Predictive Factors," *CardioVascular and Interventional Radiology* 44, no. 5 (May 2021): 758–765, https://doi.org/10.1007/s00270-020-02754-5.

23. A. Mukund, A. Aravind, A. Jindal, H. V. Tevethia, Y. Patidar, and S. K. Sarin, "Predictors and Outcomes of Post-transjugular Intrahepatic Portosystemic Shunt Liver Failure in Patients With Cirrhosis," *Digestive Diseases and Sciences* 69, no. 3 (March 2024): 1025–1034, https://doi.org/10.1007/s10620-023-08256-x.

24. R. Moreau, M. Tonon, A. Krag, et al., "EASL Clinical Practice Guidelines on acute-on-chronic Liver Failure," *Journal of Hepatology* 79, no. 2 (August 2023): 461–491, https://doi.org/10.1016/j.jhep.2023.04.021.

25. European Association for the Study of the Liver, "Electronic Address: Easloffice@easloffice.eu, European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of Alcohol-Related Liver Disease," *Journal of Hepatology* 69, no. 1 (July 2018): 154–181, https://doi.org/10.1016/j.jhep.2018.03.018.

26. T. Bucsics, S. Hoffman, J. Grünberger, et al., "ePTFE-TIPS Vs Repetitive LVP plus Albumin for the Treatment of Refractory Ascites in Patients With Cirrhosis," *Liver Int Off J Int Assoc Study Liver* 38, no. 6 (June 2018): 1036–1044, https://doi.org/10.1111/liv.13615.

27. T. Bucsics, M. Schoder, M. Diermayr, et al., "Transjugular Intrahepatic Portosystemic Shunts (TIPS) for the Prevention of Variceal Rebleeding - a Two Decades Experience," *PLoS One* 13, no. 1 (2018): e0189414, https://doi.org/10.1371/journal.pone.0189414.

28. T. Bucsics, K. Lampichler, C. Vierziger, et al., "Covered Transjugular Intrahepatic Portosystemic Shunt Improves Hypersplenism-Associated Cytopenia in Cirrhosis," *Digestive Diseases and Sciences* 67, no. 12 (December 2022): 5693–5703, https://doi.org/10.1007/s10620-022-07443-6.

29. J. Fine and R. J. Gray, "A Proportional Hazards Model for the Subdistribution of a Competing Risk," *Journal of the American Statistical Association* 94, no. 446 (1999): 496–509, https://doi.org/10.1080/01621459.1999.10474144.

30. G. Addolorato, A. Mirijello, P. Barrio, and A. Gual, "Treatment of Alcohol Use Disorders in Patients With Alcoholic Liver Disease," *Journal of Hepatology* 65, no. 3 (September 2016): 618–630, https://doi.org/10.1016/j.jhep.2016.04.029.

31. S. Faure, A. Herrero, B. Jung, et al., "Excessive Alcohol Consumption After Liver Transplantation Impacts on Long-Term Survival, Whatever the Primary Indication," *Journal of Hepatology* 57, no. 2 (August 2012): 306–312, https://doi.org/10.1016/j.jhep.2012.03.014.

32. G. E. Vaillant, P. P. Schnurr, J. A. Baron, and P. D. Gerber, "A Prospective Study of the Effects of Cigarette Smoking and Alcohol Abuse on Mortality," *Journal of General Internal Medicine* 6, no. 4 (July 1991): 299–304, https://doi.org/10.1007/bf02597425.

33. R. Bataller, G. E. Arteel, C. Moreno, and V. Shah, "Alcohol-Related Liver Disease: Time for Action," *Journal of Hepatology* 70, no. 2 (February 2019): 221–222, https://doi.org/10.1016/j.jhep.2018.12.007.

34. G. Mamone, M. Milazzo, A. Di Piazza, et al., "Transjugular Intrahepatic Portosystemic Shunt (TIPS) Complications: What Diagnostic Radiologists Should Know," *Abdom Radiol N Y* 47, no. 12 (December 2022): 4254–4270, https://doi.org/10.1007/s00261-022-03685-0.

35. R. K. Patel, K. Chandel, T. P. Tripathy, and A. Mukund, "Complications of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in the Era of the Stent Graft - What the Interventionists Need to Know?," *European Journal of Radiology* 144 (November 2021): 109986, https://doi.org/10.1016/j.ejrad.2021.109986.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: ueg270131-sup-0001-suppl-data.docx. **Figure S1:** Distribution of patients undergoing TIPS implantation by year of procedure. **Figure S2:** Comparison of biomarkers between patients with and without post-TIPS alcohol use according to Kruskal-Wallis test. (A) GGT comparison. (B) MCV comparison. **Figure S3:** Cumulative incidence of outcomes stratified by alcohol use patterns in patients undergoing TIPS for recurrent/refractory ascites. (A) Cumulative incidence of ACLF in patients undergoing TIPS for recurrent/refractory ascites. (B) Cumulative incidence of liver-related death in patients undergoing TIPS for recurrent/refractory ascites. **Figure S4:** Cumulative incidence of outcomes stratified by alcohol use patterns in patients undergoing TIPS for variceal bleeding. (A) Cumulative incidence of ACLF in patients undergoing TIPS for variceal bleeding. (B) Cumulative incidence of liver-related death in patients undergoing TIPS for variceal bleeding.