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Title: Fibrosis Severity as a Determinant of Cause-specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease.

Short title: Clinical Outcomes in Patients With Advanced NAFLD.

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Abbreviations: NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis; HIV, human immunodeficiency virus; CTP, Child-Turcotte-Pugh; MELD, Model for End-Stage Liver Disease; NAS, NAFLD activity score; US, ultrasound; CT, computed tomography; MR, magnetic resonance; sHR, subhazard ratio; HR, hazard ratio; BMI, body mass index; TACE, transarterial chemoembolization.

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ABSTRACT

Background & Aims: Little is known about the natural course of nonalcoholic fatty liver disease (NAFLD) with advanced fibrosis. We describe long-term outcomes and evaluate the effects of clinical and histologic parameters on disease progression in patients with advanced NAFLD.

Methods: We conducted a multi-national study of 458 patients with biopsy-confirmed NAFLD with bridging fibrosis (F3, n=159) or compensated cirrhosis (222 patients with Child-Turcotte-Pugh [CTP] scores of A5 and 77 patients with scores of A6), evaluated from April 1995 through November 2013 and followed until December 2016, death, or liver transplantation at hepatology centers in Spain, Australia, Hong Kong, and Cuba. Biopsies were reevaluated and scored; demographic, clinical, laboratory, and pathology data for each patient were collected from the time of liver biopsy collection. Cox proportional and competing risk models were used to estimate rates of transplant-free survival and major clinical events and to identify factors associated with outcomes.

Results: During a mean follow-up time of 5.5 years (range, 2.7–8.2 years), 37 patients died, 37 received liver transplants, 88 had initial hepatic decompensation events, 41 developed hepatocellular carcinoma (HCC), 14 had vascular events, and 30 developed non-hepatic cancers. A higher proportion of patients with F3 fibrosis survived transplant-free for 10 years (94%; 95% CI, 86–99) than of patients with cirrhosis and CTP-A5 (74%; 95% CI, 61–89) or CTP-A6 (17%; 95% CI, 6–29). Patients with cirrhosis were more likely than patients with F3 fibrosis to have hepatic decompensation (44%; 95% CI, 32–60 vs 6%, 95% CI, 2–13) or HCC (17%; 95% CI, 8–31 vs 2.3%, 95% CI, 1–12). The cumulative incidence of vascular events was higher

in patients with F3 fibrosis (7%; 95% CI, 3–18) than cirrhosis (2%; 95% CI, 0–6). The cumulative incidence of non-hepatic malignancies was higher in patients with F3 fibrosis (14%; 95% CI, 7–23) than cirrhosis (6%; 95% CI, 2–15). Death or transplantation, decompensation, and HCC were independently associated with baseline cirrhosis and mild (<33%) steatosis whereas moderate alcohol consumption associated with these outcomes only in patients with cirrhosis.

Conclusions: Patients with NAFLD cirrhosis have predominantly liver-related events whereas those with bridging fibrosis have predominantly non-hepatic cancers and vascular events.

KEY WORDS: Nonalcoholic steatohepatitis; cryptogenic cirrhosis; gastroesophageal varices; competing risk analysis.

Word count: 366 words

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of hepatocellular carcinoma (HCC), end-stage liver disease and liver transplantation worldwide.[1-5] Its prevalence is growing in parallel with the global epidemics of obesity and type 2 diabetes.[6] Although its evolution towards liver-related complications is relatively slow, approximately one third of NAFLD patients may eventually progress to nonalcoholic steatohepatitis (NASH), of whom 20% will develop hepatic fibrosis with a risk for extrahepatic complications, cirrhosis, and liver failure. [7-12]

A number of well-designed retrospective studies detailing the long-term mortality of histologically confirmed NAFLD have been published. [13-18] These reinforce the importance of fibrosis as the most robust determinant of all-cause and liver-related mortality; a dose-dependent effect has been observed across all fibrosis stages (from stage 1 to 4), however, the risk of liver-related mortality is exponentially increased while transitioning from stage 2 to 4. [14, 19, 20] Patients with bridging fibrosis and cirrhosis have the highest risk of liver-related death, however due to the high prevalence of co-morbid cardio-metabolic risk factors such as diabetes and obesity, they are also at risk of developing major vascular events and non-hepatic malignancies. Unfortunately, earlier studies have included small numbers of patients with advanced fibrosis, which makes it difficult to understand the true risk on the full spectrum of major complications. This study sought to investigate the long-term overall transplant-free survival and cumulative incidences of major clinical events (hepatic decompensation, HCC, stroke or ischemic heart disease and non-hepatic malignancies) in a large cohort of biopsy-confirmed NAFLD with advanced fibrosis followed for 10 years, and to identify potential predictors for outcomes.

METHODS

The NAFLD progression consortium (*NPC*) is an international initiative which includes tertiary academic centers with recognized experience and participation in studies related to the natural history of NAFLD. The main objective is to gather and analyse information of existing prospectively collected data of patients with biopsy-proven NAFLD.

Study design and participants.

A consortium of researchers from tertiary referral centers in Europe, Asia, Australia and America was created. Each center had independently developed a prospective data registry of consecutive biopsy-proven NAFLD patients with at least 25 or more patients with advanced fibrosis with a minimum of 1 year of follow-up. All subjects were recruited from Hepatology clinics at each center following referral from community physicians and were enrolled by the local investigator. Each center had local approval from their Institutional Review Board and signed informed consent was obtained from each patient. Some patients included in this cohort have been part of other papers published previously.[15]

Liver biopsies were performed in the presence of fatty liver detected by imaging and/or, persistently increased levels of aminotransferase for at least 6 months and/or risk factors for advanced disease (e.g. metabolic syndrome, age > 45 years, obesity, diabetes) and/or suspected advanced fibrosis or cirrhosis as determined by abnormal laboratory (low platelet count, etc.) and imaging (US, CT or MRI) tests.

Patients were excluded if they had one of the following: significant alcohol intake (> 20 g per day for men and > 10 g per day for women during the last two years or during follow-up), secondary causes of liver diseases, including viral, autoimmune, drug-induced, cholestatic, genetic or metabolic, secondary causes of NAFLD, history of

bariatric surgery, significant body weight reductions (>5%) via lifestyle changes in the last year, type 1 diabetes, known sero-positivity for HIV, Child-Turcotte-Pugh (CTP) score ≥ 7 or history of hepatic decompensation, MELD score ≥ 15 (excluding values dependent of high levels of creatinine), albumin <3.0 g/dL, total bilirubin > 3.0 mg/dL, INR >2, platelets <100,000 mm^3, concomitant diseases with reduced life expectancy, evidence of HCC at enrollment or within 6 months of follow-up and inability to provide informed consent.

A total of 512 subjects aged 18 to 80 years with histologically-confirmed NAFLD and advanced fibrosis (F3/F4) were evaluated from April 1995 to November 2013; 458 fulfilled eligibility criteria and were followed until December 2016, or death or liver transplantation (**supplementary Figure 1)**.

Histological Assessment

In all participant centers, biopsies were reevaluated and scored by local pathologists using the NASH-CRN scoring system and fibrosis (F) stages, [21, 22] independent of the original histology report. Only reports of repeated histological assessment were considered in our analyses. Pathologists were unaware of the patients' clinical and laboratory features. A threshold of at least 5% of hepatocytes showing steatosis was necessary for histological confirmation of NAFLD. Since hepatocellular injury may reduce or disappear during advanced fibrosis or cirrhosis, presence of at least ballooning and/or lobular inflammation was required for confirming NASH.[21-23] For all biopsy samples, the NAFLD activity score (NAS) and their individual components were scored as follow: steatosis (0-3), lobular inflammation (0-3) and hepatocellular ballooning (0-2). The stage of fibrosis was assessed from 0 to 4 (1: perisinusoidal or portal/periportal only; 2: perisinusoidal and periportal; 3: bridging fibrosis; 4 cirrhosis), but only F3 and F4 stages were considered for analysis in the present study.

Although reproducibility studies have shown good or excellent pathological agreement for steatosis grades (kappa, 0.79) or extent of fibrosis (kappa, 0.84), we sought to confirm the diagnostic accuracy and consistency of our initial pathological evaluations.[21] To do so, 48 random samples were selected from overall cohort and sent for central reading and scoring to Dr. Anthony Chan at The Chinese University of Hong Kong who was blinded to all study information, including previous pathological reports. Interobserver variation among pathologist was evaluated by kappa statistics. We observed high inter-rater agreement for stage of fibrosis (κ ranging from 0.80-1) and extent of steatosis (κ ranging from 0.71-0.85) Agreement was moderate for grading lobular inflammation (κ ranging from 0.44-0.63) and ballooning (κ ranging from 0.53-0.75).

Data collection, follow-up and events assessment

Demographic, clinical, laboratory, and pathological data for each patient were collected at the same time of liver biopsy. The follow-up period began on the date of biopsy and ended on the date of the last visit, death, or transplant. All patients were evaluated every 3-6 months according to local clinical standards of care and the occurrence of death or liver transplantation were the primary outcomes of interest. Patients lost to follow-up (n=4) were censored at the last date known to be alive.

A detailed medical history and physical examination along with standard laboratory tests were routinely performed at each follow-up visit. This included assessment of alcohol consumption, [24] smoking, development of diabetes or co-morbid malignancy or vascular disease. This data was collected prospectively and retrospectively following an extensive review of the patient medical record, clinic letters and laboratory results. Six-monthly liver ultrasound (US) and serum α-fetoprotein determinations were obtained to screen for HCC if the patient had cirrhosis. Diagnosis,

screening and treatment of hepatic and non-hepatic (e.g., cardiovascular disease, cancer, etc.) clinical events were implemented according to local standards-of-care. Given the absence of approved treatments for NAFLD, therapeutic recommendations were similar in all participant centers and included dietary modifications and/or increased physical activity.

The development of major clinical events over time was defined as follows: (1) hepatic decompensation defined as the first occurrence of ascites (identified by abdominal US), or upper gastrointestinal bleeding secondary to portal hypertension (confirmed by endoscopy in the presence of gastroesophageal varices or hypertensive gastropathy) or hepatic encephalopathy (established by clinical parameters, neuropsychological tests, or electroencephalogram); (2) HCC diagnosed by dynamic contrast-enhanced imaging methods (CT scan or MR) according to standard criteria[25] or biopsy; (3) major vascular events defined as the development of a new episode of cardiovascular (myocardial infarction, hospitalization for congestive failure or unstable angina, aneurysm dissection, or cardiac arrest) or cerebrovascular (ischemic or hemorrhagic stroke) disease; (4) non-hepatic malignancy (any other than HCC) excluding non-melanoma skin cancers. Each of these events was recorded when first seen, and recurrence of the same complication or occurrence of a new event pertaining to the same category was not included.

Statistical analysis

Time to any clinical outcome was computed as the number of years from enrollment to the date of the initial clinical outcome. Cox proportional hazard models were performed to estimate the adjusted hazard risks and identify independent predictors of death or transplant.

The cumulative incidence of secondary outcomes (first event of hepatic decompensation, HCC, major vascular events and non-hepatic malignancies) were calculated in the presence of competing risks events (another event has occurred, which precludes or modifies the occurrence of the event of interest).[26] To estimate effects of covariates on secondary outcomes, univariate and multivariable competing risk regression models for the sub-distribution hazards were performed according to the method of Fine and Gray.[26, 27] The strength of the association between each covariate and the outcome of interest was assessed using the subhazard ratio (sHR) with 95% CI.

Transplant-free survival rates and cumulative incidences of secondary outcomes in all cases were adjusted by center and calendar year of patient recruitment; Figures 1-3 represent adjusted predictions.

As long-term clinical outcomes may be influenced by the severity of fibrosis and liver function, analyses were stratified by fibrosis stage (F3 vs. F4) and CTP score (class A5 vs. A6).

We further reported the annualized incidence rates with their 95% confidence intervals for all outcomes. These rates were calculated by dividing the number of patients with a defined event by the number or person-years for which the subjects were followed and then multiplied by 100. Missing values were imputed by applying the multiple imputations method where missing data are imputed or replaced with a set of plausible values.[28]

All confidence intervals, significance tests, and resulting *P* values were two-sided, with an alpha level of 0.05. Statistical analyses were performed using STATA software, release 13.

RESULTS

Baseline Characteristics

Table 1 summarizes overall features of the study population. A total of 458 subjects were included, of which 159 (35%) and 299 (65%) had bridging fibrosis and cirrhosis, respectively. Most of cirrhotic patients were CTP-A5 (74%). The patients' mean age was 55.9 years and 52% were women. There was a preponderance of white race (81%), mostly Hispanic (56%). The mean BMI was 33.2 kg/m^2 and about two thirds had type 2 diabetes (67%) or hypertension (61%). The mean MELD score was 7.7 ± 2.6 and gastroesophageal varices were present in 92 (20%) individuals. Overall, 39 (9%) and 22 (5%) patients had a previous history of vascular diseases and malignant neoplasms, respectively. The mean NAS was 4.2 ± 1.9 and 199 (43%) subjects had a NAS ≥ 5. The median biopsy length and portal tracts were 18 mm (IQR: 15-23) and 9 (IQR: 8-11), respectively. Three-hundred and ninety-four (86%) biopsy samples had a length of at least 15 or more millimeters and 123 (27%) had less than 10 portal tracts. [29, 30] As shown in **Table 1**, clinical and biochemical data related to severity of liver disease were worse in cirrhotic patients and more severe in those with CTP class A6 than those with A5. Elevated levels of INR (1.7-2) but mainly bilirubin (2-3 mg/dl) or albumin (3.0-3.5) would explain the main differences found between compensated patients with CTP A5 vs A6 (**supplementary Table 1**). Although cirrhotic patients tended to have a higher mean 10-y risk score for heart/stroke disease[31] (F4-A5: 13.9 vs. F4-A6: 13.5 vs. F3: 11.4, P=0.12), other well-recognized risks factors for vascular disease such as total cholesterol and LDL cholesterol levels and systolic/diastolic blood pressures were lower than in non-cirrhotic patients (all P<0.05). Interestingly, cirrhotic patients with CTP-A6 had less inflammation and steatosis (steatosis < 33% [53, 69%], none or few lobular inflammation [69, 77%] and none or few ballooned cells [64, 83%)] than subjects with F3 or F4-A5, (P<0.01). **Supplementary Table 2** summarizes key baseline

characteristics between countries. Only BMI and waist circumference values were significantly different (lowest) in cohorts from Hong Kong and Cuba as compared with the remaining cohorts after adjustments for fibrosis severity and CTP scores (**supplementary appendix** and **Table 1)**.

Time-Dependent Characteristics

Eleven (17%) of the 66 patients with a baseline level of moderate (between 1-70 g/week for women and 1-140 g/week for men) alcohol intake became abstinent over the course of follow-up. No heavy or new-onset drinkers were recorded during follow-up. New-onset type 2 diabetes was detected in 21 (14%) of 153 subjects without diabetes at baseline, with no significant difference observed between patients with bridging fibrosis and cirrhosis (P=0.17). Of 77 patients reported as current smokers at baseline, 62 were still smoking while all non-smoker participants remained as non-smokers over time.

Overall survival without liver transplantation

The overall mean follow-up period was 5.5 years (range, 2.7-8.2). Overall causes of death, occurrence of major clinical events and their annualized rates are summarized in **Table 2, 3** and **supplementary appendix, Table 3.**

During follow-up, 74 patients died (37 [8%]) or were transplanted (37 [8%]). The major causes of death were liver-related (F4-A6: 18 vs. F4-A5: 11 vs. F3: 2) and 6 were non-liver-related (F4-A6: 0 vs. F4-A5: 4 vs. F3: 2). Most liver-related deaths were attributable directly to complications of end-stage liver disease, where hepatorenal syndrome and HCC were the commonest causes. Three (50%) of six non-liver-related deaths were from vascular events. Hepatic decompensation (26 patients, 70%) was the main indication for liver transplantation followed by HCC (6 subjects [16%]) and the combination of end-stage renal-hepatic failure (5 patients [14%]). Ten-year overall

transplant-free survival rate was 68% (95% CI: 53-75); 94% (95% CI: 86-99) in F3, 74% (95% CI: 61-89) in F4-A5 and 17% (95% CI: 6-29) in F4-A6 patients (P<0.01), which is equivalent to annualized mortality/liver transplantation rates of 0.5, 2.1 and 11.1 per 100 person-years, respectively, P<0.01 (**Figure 1 and Table 3**).

Cumulative incidence of a first major clinical event

The 10-year cumulative rates for a first major clinical event were notably higher in cirrhotic patients with CTP-A6 (92%, 95% CI: 80-99) than subjects with F4-A5 (60%, 95% CI: 48-73) and F3 (30%, 95% CI: 21-49), P<0.01 (**supplementary appendix, Figure 4)**. Hepatic decompensation (85% and 59%) and HCC (15% and 19%) were the commonest first events seen in cirrhotic patients with CTP-A6 and A5 respectively, in contrast to non-hepatic malignancies (38%) and vascular events (35%) that were the most frequently observed in F3 patients (**Table 2**).

Liver-related events

During 10 years of follow-up, 88 (19%) and 41 (9%) patients developed an episode of hepatic decompensation or HCC, respectively. Ascites (62 of 88, 70%) and variceal bleeding (21 of 88, 24%) were the most common causes of decompensation. At the time of HCC diagnosis, 31 (76%) of 41 were detected in very early or early stages, and of them, 22 were treated with curative treatments (ablation, n=19 or resection, n=3) and 9 with liver transplant. Six and four patients were diagnosed in intermediate and advanced stages and were treated with TACE or sorafenib respectively. Six of them died due to HCC. Half of patients with HCC development (22 of 41, 51%) had a previous episode of hepatic decompensation during follow-up.

Cirrhotics were more likely to develop hepatic decompensation (44%, 95% CI: 32-60) and HCC (17%, 95% CI: 8-31) than those with bridging fibrosis (decompensation: 6%

[95% CI: 2-13], HCC: 2.3% [95% CI: 1-12]), P<0.01. Among cirrhotic patients, CTP-A6 showed highest CIs of hepatic decompensation (84%, 95% CI: 72-95) and HCC (37%, 95% CI: 22-49) as compared to CTP-A5 (decompensation: 30%, 95% CI: 19-46; HCC: 16%, 95% CI: 10-26), P<0.01. The annualized rates for hepatic decompensation and HCC were 15.6 and 4.7 in F4-A6, 3.3 and 1.8 in F4-A5 and 0.6 and 0.2 in F3 subjects, respectively (**Figure 2A-B and Table 3**).

Major vascular events and non-hepatic malignancies

A total of 14 (3%) vascular events occurred over time, of which 10 (71%) and 4 (29%) were related to cardiac and cerebrovascular diseases, respectively. Only 3 (21%) patients died due to vascular events. The cumulative incidence of developing any vascular event was considerably higher in subjects with F3 (7%, 95% CI: 3-18) than F4 (2%, 95% CI: 0-6), adj. Fine and Gray P<0.01 and no difference was found among cirrhotic patients with CTP A5 and A6 (**Figure 2C**).

As shown in Table 2, 30 (7%) patients developed at least one non-hepatic malignant neoplasm. The most frequent neoplasm was colorectal cancer seen in 15 cases (50%), followed by skin (6, 20%), breast (3, 10%), and uterine (2, 7%) cancers. Two patients died due to metastatic colorectal cancer. After excluding skin cancers due to low causality relationship with NAFLD, the cumulative incidence of non-hepatic malignant neoplasia was numerically higher in F3 subjects (14%, 95% CI: 7-23) than F4-A5 (7%, 95% CI: 2-15) and F4-A6 (4%, 95% CI: 1-10) individuals, however, no significant differences were observed among groups, adj. P=0.10 (**Figure 2D**).

Predictors of overall mortality and major clinical outcomes

Demographic, clinical and biochemical predictors

Univariate association between potential predictors and transplant-free survival and liver-related outcomes is shown in **supplementary Table 4**.

At multivariable analysis (**Table 4),** age and male sex were positively associated with worse survival (HR for age: 1.03, HR for male: 1.87) and greater incidence of HCC (sHR for age: 1.05, sHR for male: 7.28). Current smoking was also associated with a higher risk of mortality (HR: 1.74) and HCC (sHR: 2.11). Type 2 diabetes was a robust predictor of poor transplant-free survival (HR: 3.33) and liver-related outcomes (sHR for decompensation: 2.82, sHR for HCC: 4.72).

Gastroesophageal varices at baseline was associated with worse survival (HR: 2.19) and higher rates of hepatic decompensation (sHR: 1.99) and MELD score remained an important predictor of long-term survival (HR: 1.10), **Table 4**. Other factors strongly related with severity of liver disease such as albumin, INR, bilirubin, and platelets were also associated with transplant-free survival and decompensation. **Table 4** summarizes association between potential predictors, transplant-free survival and liver-related outcomes.

Interestingly, moderate alcohol consumption was found to increase risk of death or transplant (HR 2.3, 95% CI: 1.32-4.02), decompensation (HR: 1.65, 95% CI: 1.01-2.61) and HCC (HR 3.22, 95% CI: 1.64-6.32) among cirrhotic patients even after adjustments by CTP score and other potential confounders, all $P<0.05$. No association was found between liver-related outcomes and moderate alcohol intake among patients with bridging fibrosis. Likewise, no relationship was observed between non-hepatic outcomes and alcohol consumption. Supplementary **Table 5 and Figure 5 A-C** illustrate the association between alcohol consumption and study outcomes.

Histological predictors

Overall, cirrhosis negatively affected survival rates (HR: 5.99) and liver-related outcomes (sHR for decompensation: 6.55; sHR for HCC: 6.52), but was associated with lower frequency of vascular events (sHR: 0.25). Although lower scores of steatosis,

lobular inflammation and ballooning were inversely associated with fibrosis severity and CP score (**Table 1**), only steatosis < 33% was consistently associated with worse survival (HR: 2.56) and liver-related events (sHR for decompensation: 2.64, sHR for HCC: 2.21) even after adjustments for potential demographic and clinical confounders (**supplementary Table 6**). Given the magnitude of the association between steatosis < 33% and severity of liver disease, we explored the relative importance of combining both variables on major clinical outcomes in cirrhotic patients. As shown in **Figure 3A**, patients within the same class of CTP and steatosis < 33% had worse survival than those with steatosis ≥ 33%, P<0.01. However, the "protective" association of steatosis ≥ 33% on development of hepatic decompensation was limited to subjects with CTP-A5, P<0.01 (**Figure 3B**). HCC rates were higher in patients with steatosis < 33% irrespective of CTP score class, P<0.01 (**Figure 3C**). While an unadjusted analysis showed higher rates of HCC in subjects with CTP-A6 compared with CTP-A5, no significant differences were observed between these two subgroups after adjusting by steatosis < 33%, sHR: 0.56. We did not find any association between steatosis severity and vascular event rates (**data not shown**).

Predictors of major vascular events

Regarding major vascular events, older age (sHR: 1.05), diabetes (sHR: 2.15), baseline BMI (sHR: 1.07) and LDL cholesterol levels (sHR: 1.06) were independently associated with the occurrence of any major vascular event over time (**supplementary Table 7**). No significant association was found between baseline 10-y heart/stroke risk score, moderate alcohol consumption or smoking and the incidence of vascular events, although the number of vascular events were relatively low.

DISCUSSION

This study identifies new information on the clinical course of NAFLD patients with advanced fibrosis based on three stages of disease with distinctly different outcomes.

The current data shows that among NAFLD patients with advanced fibrosis, those with cirrhosis are at a significantly greater risk for hepatic decompensation, HCC and death or liver transplantation as compared to those with bridging fibrosis. Among cirrhotic patients, hepatic decompensation (70%) was the most commonly identified initial clinical event, followed by HCC development (17%); both were linked to profound effects on survival rates and the requirement for liver transplantation. In contrast, patients with bridging fibrosis showed a more benign clinical course with higher transplant-free survival (94%) and less liver-related complications than those with cirrhosis. Vascular events (35%) and non-hepatic malignancies (38%) accounted for two thirds of all major initial events in these subjects. Although overall mortality was significantly lower in bridging fibrosis, 50% (2 of 4) of deaths were directly attributed to vascular events or non-hepatic cancers. In contrast, patients with cirrhosis were at significantly lower risk for non-liver related complications (14 [12%] of 115 initial events) and deaths (4 [12%] of 33).

Among Childs class A cirrhotics, hepatic outcomes were dramatically worse among those with CTP-6 versus CTP-5, despite both groups being compensated at baseline. Results of previous studies have confirmed that patients with significant or advanced fibrosis (F2-F3) are at higher risk of vascular events and cancers as compared with subjects without significant fibrosis (F0-F1). Taken as a whole, previous and current findings highlight the importance of underlying fibrosis stage in determining clinical outcomes and cause-specific mortality.[7, 14, 32, 33]

The co-existence of obesity, metabolic syndrome, and diabetes among advanced stage NAFLD patients can trigger cardiovascular events and cancers. In this regard, the relatively low rates of vascular events and non-hepatic malignancies was not anticipated and is noteworthy. While bridging fibrosis progresses to cirrhosis and to impairment of liver function, blood pressure, cholesterol levels and body weight tend to decrease (as shown in **Table 1**) which may partly explain the lower rates of vascular events in cirrhotic patients. However, this finding does not easily explain the low rate of non-hepatic cancers. Another potential explanation for our observations is that higher liver related competing mortality or transplantation in cirrhotic patients may have precluded the development of vascular events and non-hepatic cancers over time.

Although fibrosis stage was biopsy-confirmed in all patients, 7 (4%) with bridging (F3) fibrosis had gastroesophageal varices at study entry. This suggests that there could be some misclassification and underscores the limitations inherent with liver biopsy. Notably, the recent Baveno consensus recommended the term of compensated advanced chronic liver disease (cACLD) which may include bridging fibrosis and cirrhosis and identifies patients at risk of developing clinically significant portal hypertension. [34] cACLD is suspected with a high liver stiffness measurement and confirmed with biopsy, endoscopy or hepatic venous pressure gradient assessment.

Another key finding was that the outcomes among cirrhotics were worse in patients with CTP class A6 as compared with A5. CTP-A6 patients were at highest risk of hepatic decompensation, HCC and death or transplant. At 10 years, three quarters of CTP-A6 patients had either died or required a liver transplant compared to one in five CTP-A5 patients and only one in 25 patients with baseline bridging fibrosis. Interestingly, a low albumin was the commonest biochemical abnormality in CTP- A6 patients in the absence of clinically manifest decompensation. While patients with

bridging fibrosis have lower probabilities of liver-related outcomes within the first 10 years of follow-up, the greater likelihood of vascular events and non-hepatic malignancies suggests surveillance and prevention strategies for these outcomes should be prioritized as part of their management. In contrast, compensated cirrhotic patients, and most importantly those with CTP-A6 had the worst survival, mandating close monitoring to prevent and control liver-related events. These findings are also particularly relevant for the design and interpretation of clinical trials.

Previous long-term follow-up studies have reported increased rates of liver-related outcomes among NAFLD patients with cirrhosis, [15, 35-38], however, the time-course of events were not reported, one of them included solely decompensated cirrhotic patients[35], no major comparisons were performed for all outcomes among F3 and F4 patients[15], and all studies were underpowered to detect robust predictors for death,[15] decompensation[15] or HCC[15, 35]. In the study of Bhala and colleagues, 7.7% and 2.4% of patients with F3 or F4 developed hepatic decompensation or HCC during an average of 85.6 months.[15] Likewise, Ascha, et al. reported that NASH-cirrhotic patients are at increased risk of developing HCC, and the annual cumulative incidence of HCC was found to be 2.6% in patients NASH-cirrhosis compared with 4.0% in patients with HCV-related cirrhosis.[35]

In this study, HCC development appeared mostly in cirrhotic patients, being less frequent in subjects with bridging fibrosis. The presence of higher rates of HCC in cirrhotics with CTP-A6 suggest the need for greater vigilance and perhaps more rigorous screening approaches.[39, 40]

Our data interestingly suggested that steatosis < 33% is significantly associated with a higher risk of death and liver-related complications including HCC, and this effect was particularly marked in cirrhotic patients even after adjustments for potential

confounders such as CTP score. Patients within the same class of CTP with steatosis < 33% had shorter survival and higher risk of decompensation and HCC than those with steatosis ≥ 33%. As shown in **supplementary Table 8**, steatosis < 33% was associated with lower BMI, marked impairment in liver function tests and reduced values of serum lipids which have been associated with liver dysfunction and malnutrition in cirrhotic patients. Data from previous clinical studies suggest that cirrhotic-NASH patients often have a significant reduction in hepatic fat, a phenomenon known as "burnt-out" NASH. Increased utilization of fat stores (including in liver) due to an increased catabolic state, diversion of insulin and nutrients from the liver due to portal hypertension and increased levels of adiponectin have been postulated as potential pathways to explain the reduced levels of hepatic lipids in these subjects.[41] Van der Poorten, *et al*. found that in NASH patients with advanced fibrosis, high circulating adiponectin [42] were associated with hepatic fat loss irrespective of metabolic and liver dysfunction.[41] In another interesting study, adiponectin levels were significantly elevated in cirrhotic patients and the level of adiponectin increased proportionately with the Child-Pugh score.[43] Adiponectin levels have been inversely associated with the risk of developing cancer and coronary heart disease [44-46]. Thus, the hypothesis that hyperadiponectinemia seen in NASH-cirrhosis could be protective for HCC and coronary heart disease risk needs to be explored. Our data lends support to this hypothesis of steatosis < 33% being an indirect marker of liver disease severity, hyperadiponectinemia and probably of malnutrition in compensated NASH cirrhosis.

Our findings support previous studies indicating that older age, male gender and current smoking are common risk factors for HCC development.[47-49]

Previous epidemiological data suggests that slight or moderate alcohol intake may have favorable hepatic effects among NAFLD patients, [24, 50] However, a recent

longitudinal study that examined the association of alcohol consumption and the histological evolution of NAFLD histology in patients with paired biopsies found that modest alcohol consumption was associated with less improvement in NASH and steatosis compared to non-alcohol intake [51]. The influence on liver-related outcomes among NAFLD patients however has not been examined in longitudinal studies. Our data indicates that moderate alcohol consumption among compensated NASH cirrhotic patients may exacerbate the progression of liver disease and increase the risk of hepatic decompensation, HCC and death. In compensated HCV-related cirrhosis, moderate alcohol consumption has also been linked to increased risk of HCC.[52] In contrast to findings in the general population, moderate alcohol use may not reduce the risk of cardiovascular events in patients with NAFLD.[53] Thus, NAFLD patients, in particular those with cirrhosis, should be strongly advised to avoid any alcohol intake.

Although a low number of vascular events occurred over time, we sought to identify its potential predictors. Diabetes, larger BMI, older age and higher LDL cholesterol levels were positively associated with the occurrence of ischemic heart and cerebrovascular diseases. These findings suggest that intensive control of these and other well-recognized risk factors for vascular disease may have been implemented, irrespective of liver disease severity.

It's important to address some limitations of this study. Firstly, we presented the cumulative incidence of each outcome occurring from each stage (F3 vs. F4 with CTP-A5 vs. F4 with CTP-A6) as defined at study enrollment, without accounting for transition across stages over time. Second, prospective information on dynamic changes in metabolic and lipid parameters as well as pharmacological interventions for obesity-related comorbidities and the compliance to standardized protocols for diagnosing and treating clinical events were not documented. Third, our study failed to obtain central

pathological reading of all liver samples. Lastly, our cohort was derived from tertiary referral centers and consisted of patients who underwent liver biopsy, and thus may be biased towards more severe disease.

CONCLUSION

NAFLD patients with biopsy-proven cirrhosis have a higher mortality and liver-related complications than those with bridging fibrosis, whereas vascular events and non-hepatic malignancies are the commonest complications in those with bridging fibrosis. Patients with diabetes were at high risk group for both liver and vascular outcomes. Moderate alcohol consumption significantly increases risk of hepatic decompensation, HCC and liver-related death in cirrhotic patients. Steatosis severity was inversely related to liver disease severity and constituted an important predictor of survival and hepatic outcomes.

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TABLES

Table 1. Baseline characteristics.

Variable	Overall N=458	Bridging fibrosis n=159	Cirrhosis CTP A5 n=222	Cirrhosis CTP A6 n=77	*P* value
Age (y)	55.9 ± 11.2	54.2 ± 10.7	56.6 ± 11.8	57.4 ± 10.4	.04
Male, n (%)	218 (48)	79 (50)	99 (46)	40 (52)	.43
Race/ethnicity					<.01
Hispanic White	256 (56)	76 (48)	123 (55)	57 (74)	
Non-Hispanic White	112 (24)	45 (28)	49 (22)	18 (23)	
Asian	86 (19)	38 (24)	46 (21)	2 (3)	
Black	4 (1)	0 (0)	4 (2)	0 (0)	
Former smoking, n (%)	59 (13)	25 (16)	24 (11)	10 (13)	.73
Current smoking, n (%)	78 (17)	26 (16)	39 (18)	13 (17)	.84
Alcohol consumption, n (%)					<.01
Non-drinkers	392 (86)	142 (89)	192 (86)	58 (75)	
Moderate drinkers (1-70 g/week women, 1-140 g/week men).	66 (14)	17 (11)	30 (14)	19 (25)	
BMI (kg/m^2)	33.2 ± 8.6	35.1 ± 10.6	32.3 ± 7.1	31.6 ± 6.7	<.01
Waist (cm)	106.6 ± 15.9	108.1 ± 15.9	106.1 ± 15.8	105.3 ± 15.7	.34
MELD score	7.7 ± 2.6	6.6 ± 1.11	7.5 ± 2.29	10.8 ± 3.32	<.01
Gastroesophageal varices, n (%)	92 (20)	7 (4)	49 (22)	37 (47)	<.01
History of hypertension, n (%)	281 (61)	97 (61)	136 (61)	48 (62)	.98
Systolic blood pressure (mm/Hg)	134.3 ± 17.2	137.5 ± 16	133.8 ± 15.9	129.4 ± 16.4	<.01
Diastolic blood pressure (mm/Hg)	81.6 ± 10.5	83.5 ± 11.9	81.3 ± 9.2	78.8 ± 10.3	<.01

Type 2 diabetes, n (%)	305 (67)	93 (58)	156 (70)	56 (73)	.03
Insulin, n (%)	111 (24)	24 (15)	62 (28)	25 (32)	<.01
Metformin, n (%)	177 (39)	66 (42)	90 (41)	21 (27)	.04
Sulfonylurea, n (%)	96 (21)	35 (22)	47 (21)	14 (18)	.78
DDP-4 inhibitors, n (%)	20 (4)	12 (8)	6 (3)	2 (3)	.23
SGLT2 inhibitors, n (%)	9 (2)	3 (2)	4 (2)	2 (3)	.85
Glitazones, n (%)	15 (3)	8 (5)	6 (3)	1 (1)	.42
Vitamin E, n (%)	6 (1)	4 (3)	2 (1)	0 (0)	.61
ALT (U/L)	65.3 ± 47.4	70 ± 40.7	62 ± 46.3	64.9 ± 41.3	.51
AST (U/L)	59.8 ± 43.5	56.9 ± 35.1	53.3 ± 36.3	85.5 ± 77.4	<.01
AST/ALT ratio	1.04 ± 0.46	0.92 ± 0.47	1 ± 0.39	1.39 ± 0.49	<.01
γ-Glutamyl transferase (U/L)	143.4 ± 109.2	142.6 ± 111.2	143.4 ± 99.4	145.2 ± 121.4	.99
Ferritin (ng/ml)	370.5 ± 289.2	444.3 ± 135.5	352.1 ± 165.1	272.4 ± 113.9	.03
Fasting glucose (mg/dl)	139.2 ± 62.2	126.1 ± 39.1	143.9 ± 61.2	152.7 ± 68.9	<.01
HbA1c (%)	6.96 ± 1.89	6.66 ± 1.42	7.10 ± 2.1	7.15 ± 2.08	.04
Fasting insulin (mIU/L**)**	21.4 ± 11.6	19.7 ± 8.9	21.6 ± 13.1	24.4 ± 11.5	.01
HOMA-IR	8.2 ± 7.4	6.6 ± 4.4	8.7 ± 7.4	10.1 ± 8.4	<.01
Cholesterol (mg/dl)	181.6 ± 52.2	192.1 ± 49.7	179.6 ± 51.6	165.6 ± 54.8	<.01
HDL cholesterol (mg/dl)	44.7 ± 11.6	45.9 ± 11.8	44.7 ± 12.1	42 ± 9.1	.05
LDL cholesterol (mg/dl)	104.7 ± 44.7	107.4 ± 42.6	105.8 ± 45.3	95.7 ± 46.6	.04
Triglycerides (mg/dl)	167.3 ± 91.7	182 ± 113.2	161.6 ± 75.5	153.4 ± 81.1	.03
Statin therapy, n (%)	110 (24)	42 (26)	55 (25)	13 (17)	.26
Total bilirubin (mg/dl)	0.83 ± 0.67	0.58 ± 0.21	0.75 ± 0.34	1.55 ± 0.88	<.01
Albumin (g/dl)	4.16 ± 0.43	4.28 ± 0.34	4.19 ± 0.16	3.81 ± 0.57	<.01
INR	1.09 ± 0.31	1.01 ± 0.04	1.04 ± 0.07	1.34 ± 0.37	<.01

Platelets (x 10^9/L)	184 ± 69	215 ± 67	181 ± 60	128 ± 51	<.01
α-fetoprotein (ng/ml)	3.62 ± 1.79	3.54 ± 2.05	3.52 ± 1.55	4.02 ± 1.84	.09
Creatinine (mg/dl)	0.89 ± 0.40	0.82 ± 0.23	0.92 ± 0.43	0.94 ± 0.54	.02
eGFR, mL/min/1.73m^2	87.7 ± 22.8	92.1 ± 20.6	85.1 ± 23.4	85.6 ± 23.8	<.01
eGFR <60 mL/min/1.73m^2	58 (13)	13 (8)	33 (15)	12 (16)	.04
History of vascular diseases, n (%)	39 (9)	14 (9)	18 (8)	7 (9)	.95
History of malignancies, n (%)	22 (5)	14 (9)	6 (3)	2 (3)	.04
Aspirin therapy, n (%)	24 (5)	11 (8)	10 (5)	3 (4)	.08
NAFLD fibrosis score	0.28 ± 1.58	-0.22 ± 1.59	0.20 ± 1.44	1.55 ± 1.20	<.01
FIB-4	2.71 ± 2.05	1.96 ± 1.35	2.45 ± 1.50	4.99 ± 2.86	<.01
10-y heart/stroke risk score [a]	12.9 ± 11.1	11.4 ± 10.1	13.9 ± 11.2	13.5 ± 11.6	.12
Biopsy length (mm)	18.9 ± 5.1	19.1 ± 5.2	19.1 ± 5.4	18 ± 3.8	.21
Portal tracts (n)	9.7 ± 2.9	10.1 ± 3.6	9.6 ± 2.6	9.1 ± 1.7	.09
NAS	4.2 ± 1.9	4.4 ± 1.8	4.3 ± 1.8	3.2 ± 1.7	<.01
NAS distribution, n (%) [b]					<.01
< 3	85 (19)	26 (16)	35 (16)	24 (31)	
3-4	174 (38)	56 (35)	81 (36)	37 (48)	
≥ 5	199 (43)	77 (49)	106 (48)	16 (21)	
Steatosis	1.77 ± 0.87	1.99 ± 0.85	1.77 ± 0.81	1.28 ± 0.88	<.01
<33%	181 (40)	42 (26)	86 (39)	53 (69)	<.01
Lobular inflammation	1.34 ± 0.83	1.37 ± 0.85	1.37 ± 0.85	1.16 ± 0.74	.12
None or < 2 foci per 200x field	258 (56)	83 (52)	116 (52)	69 (77)	<.01
Ballooning	1.05 ± 0.73	1.05 ± 0.69	1.11 ± 0.74	0.79 ± 0.61	<.01
None or few cells	323 (71)	120 (75)	139 (63)	64 (83)	<.01
Country, n (%)					<.01

Spain [c]	184 (40)	66 (41)	77 (34)	41 (53)
Australia [d]	116 (25)	48 (30)	50 (23)	18 (23)
Hong-Kong	82 (18)	35 (22)	45 (20)	2 (3)
Cuba	76 (17)	10 (7)	50 (23)	16 (21)

Abbreviations: **CTP**, Child-Turcotte-Pugh, **BMI**, body mass index; **MELD**, Model for End-Stage Liver Disease; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **HbA1c**, glycated hemoglobin; **HOMA-IR**, Homeostatic Model Assessment of Insulin Resistance; **INR**, international normalized ratio; **HDL**, high-density lipoprotein; **LDL**, low-density lipoprotein; **eGFR**, estimated glomerular filtration rate; **NAFLD**, nonalcoholic fatty liver disease; **NAS**, NAFLD activity score.

Quantitative data were expressed as mean ± SD.

For all laboratory measures and for continuous demographics: One-way ANOVA test with Bonferroni adjustments.

Proportions: percentage, Mantel-Haenszel Chi-Square test for trend.

The eGFR was computed by EPI-CKD formula.

[a] The 10-year risk of heart disease or stroke using the ASCVD algorithm.[31]

[b] NAS indicates NAFLD activity score. It was defined as the unweighted sum of the scores for steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2); thus, ranging from 0 to 8.

[c] Patients of two Spanish centers were recruited (Hospital Universitario Virgen del Rocio, Seville, Spain [164 patients] and Hospital Clinico Universitario de Valladolid, Valladolid, Spain [30 patients].

[d] Patients of two Australian centers were recruited (School of Medicine and Pharmacology, The University of Western Australia, Nedlands, Australia [90 patients] and Sydney Medical School, Storr Liver Centre, The Westmead Institute for Medical Research, Sidney, Australia [26 patients].

Table 2. Clinical outcomes during the follow-up based on fibrosis stages and CTP classes.

Clinical outcomes	Overall n=458 N (%)	Bridging fibrosis n=159 N (%)	Cirrhosis CTP A5 n=222 N (%)	Cirrhosis CTP A6 n=77 N (%)
Overall mortality or liver transplant	74 (16)	4 (3)	25 (11)	45 (58)
Deaths	37 (50)	4 (100)	15 (60)	18 (40)
Liver-related	31 (85)	2 (50)	11 (73)	18 (100)
Non-liver-related	6 (15)	2 (50)	4 (27)	0 (0)
Liver transplantation	37 (50)	0 (0)	10 (40)	27 (60)
First occurrence of a major clinical event [a]	141 (31)	26 (16)	63 (28)	52 (66)
Hepatic decompensation	86 (61)	5 (19)	37 (59)	44 (85)
HCC	22 (16)	2 (8)	12 (19)	8 (15)
Non-hepatic malignant neoplasms	20 (14)	10 (38)	10 (16)	0 (0)
Major vascular events	13 (9)	9 (35)	4 (6)	0 (0)
First event of hepatic decompensation	88 (19)	5 (3)	38 (17)	45 (58)
Ascites	62 (70)	2 (40)	27 (71)	33 (73)
Variceal hemorrhage	21 (24)	3 (60)	8 (21)	10 (22)
Hepatic encephalopathy	5 (6)	0 (0)	3 (8)	2 (5)
Hepatocellular carcinoma	41 (9)	2 (1)	21 (9)	18 (23)
Total major vascular events	14 (3)	8 (5)	5 (2)	1 (1)
Heart ischemic disease	10 (71)	7 (88)	3 (60)	0 (0)
Stroke	4 (29)	1 (12)	2 (40)	1 (100)
Total non-hepatic malignancies [b]	30 (7)	13 (8)	10 (5)	7 (9)
Lost to follow-up	4 (1)	1 (1)	3 (1)	0 (0)

Abbreviations: **CTP**, Child-Turcotte-Pugh; **HCC**, hepatocellular carcinoma.

[a] It includes the occurrence of a first major clinical event during follow-up period. Subsequent events were not accounted for.

[b] Colorectal cancer, 15; skin cancer, 6 (5 basal cell carcinoma and 1 melanoma); esophageal cancer, 1; lung cancer, 1; pancreatic cancer, 1; cholangiocarcinoma, 1; uterine cancer, 2; breast cancer, 3.

Table 3. Annualized incidence rates of each clinical outcome according to fibrosis stages and CTP classes.

Variable	Bridging fibrosis n=159			Cirrhosis and CTP A5 n=222			Cirrhosis and CTP A6 n=77		
	No.	Rates	95% CI	No.	Rates	95% CI	No.	Rates	95% CI
All deaths or transplantations	4	0.5	0.2-1.2	25	2.1	1.4-3.1	45	11.1	8.3-14.8
First occurrence of major clinical outcomes	26	3.2	2.2-4.7	63	5.9	4.6-7.6	52	18.3	13.9-24
First occurrence of hepatic decompensation	5	0.6	0.2-1.4	38	3.3	2.4-4.6	45	15.6	11.7-20.9
Development of hepatocellular carcinoma	2	0.2	0.02-0.9	21	1.8	1.1-2.7	18	4.7	3.0-7.5
Total major vascular events [a]	8	0.9	0.5-1.8	5	0.4	0.2-1.0	1	0.2	0.03-0.6
Total non-hepatic malignancies	10	1.2	0.6-2.2	10	0.8	0.4-1.5	3	0.7	0.2-1.4

[a] Major vascular events included cardiovascular, cerebrovascular, and arterial peripheral diseases.

Recurrence of clinical events and skin cancers were not computed for analysis purpose.

Table 4. Variables found as significant predictors of overall mortality or transplant, hepatic decompensation and hepatocellular carcinoma. Results based on multivariable Cox or competing risk regression models.

Variable	**Overall mortality/transplant** [a] n=74		**Hepatic decompensation** [b] n=88		**Hepatocellular carcinoma** [b] n=41	
	Multivariable		Multivariable		Multivariable	
	HR (95% CI)	*P*	sHR (95% CI)	*P*	sHR (95% CI)	*P*
	Model 1 (including severity of fibrosis)[c]					
Cirrhosis (yes)	5.99 (2.12-16.9)	<.01	6.55 (2.53-16.96)	<.01	6.52 (1.38-30.8)	<.01
	Model 2 (including CTP score and F3 as reference)[d]					
CTP score A5	3.83 (1.30-11.23)	<.01	4.47 (1.76-12.79)	<.01	6.7 (1.4-32.07)	<.01
CTP score A6	21.26 (6.98-64.8)	<.01	19.42 (7.03-53.67)	<.01	8.15 (1.57-42.09)	<.01
	Model 3 (including steatosis < 33%)[e]					
Steatosis < 33% (yes)	2.56 (1.35-4.82)	<.01	2.64 (1.39-5.03)	<.01	2.21 (1.14-3.79)	<.01
	Model 4 (including other potential predictors)[f]					
Age, y	1.03 (1.01-1.06)	.01	-	-	1.05 (1.01-1.10)	.01
Gender (male)	1.87 (1.08-2.85)	.04	-	-	7.28 (3.1-17.1)	<.01
Current smoking (yes)	1.74 (1.03-2.98)	.03	-	-	2.11 (1.17-5.27)	.01
Type 2 diabetes (yes)	3.33 (1.69-6.54)	<.01	2.82 (1.54-5.15)	<.01	4.72 (2.13-10.45)	<.01
INR	7.19 (3.09-16.7)	<.01	4.34 (1.41-13.33)	.01	-	-
Total bilirubin (mg/dl)	1.62 (1.19-2.21)	<.01	1.7 (1.4-2.1)	<.01	-	-
Platelet (x 10^9 L)	0.99 (0.98-0.99)	.02	0.98 (0.97-0.99)	.01	-	-
Albumin (g/dl)	0.56 (0.30-0.91)	.05	0.47 (0.26-0.88)	.01	-	-
AST/ALT ratio	1.86 (1.12-3.09)	.01	1.56 (1.03-2.98)	.03	-	-
MELD score	1.10 (1.02-1.18)	<.01	-	-	-	-

GE varices (yes)	2.19 (1.13-3.71)	<.01	1.99 (1.16-3.05)	.01	-	-

Abbreviations: **CTP**, Child-Turcotte-Pugh; **CI**, confidence interval; **sHR**, subhazard ratios; **MELD**, Model for End-Stage Liver Disease; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **GE**, gastroesophageal.

[a] Multivariable Cox regression models.

[b] Multivariable competing risk regression models.

[c] Multivariable analyses for model 1 (see supplementary Table 11) were adjusted by center, race/ethnicity, age, gender, calendar year of patients' recruitment, baseline BMI, hypertension, history of previous vascular events or malignant neoplasm, anti-diabetic, antihypertensive and hypolipidemic drugs and aspirin. Current smoking and diagnosis of type 2 diabetes were included as time-varying covariates.

[d] Multivariable analyses for model 2 (see supplementary Table 12) were adjusted by the same variables than model 1.

[e] Multivariable analyses for model 3 (see supplementary Table 13) were adjusted by the same variables than model 1 plus other liver-related tests such as INR, bilirubin, albumin, AST/ALT ratio and platelet count and excluding fibrosis severity on liver histology and CTP score.

[f] Multivariable analyses for model 4 (see supplementary Table 14) included other variables that were significant at univariate analysis (supplementary appendix, Table 4) while adjusting by fibrosis severity at baseline, center, race/ethnicity, calendar year of patients' recruitment, gender, baseline BMI, hypertension, anti-diabetic, antihypertensive and hypolipidemic drugs, aspirin, history of previous vascular events or malignant neoplasm and steatosis.

Type 2 diabetes and current smoking were analyzed as time-dependent covariates.

FIGURES

Fig. 1. Adjusted [a] overall survival without transplant according to fibrosis stage and CTP class.

[a] Survival curves correspond with adjusted predictions calculated from the Cox proportional regression model while adjusting by center and calendar year of patient recruitment.

Fig. 2. Adjusted [a] cumulative incidences of the first occurrence of major clinical outcomes according to fibrosis stage and CTP class.

(A) Hepatic decompensation.

(B) Hepatocellular carcinoma.

(C) Major vascular events

(D) Non-hepatic malignant neoplasm

[a] Cumulative incidence curves corresponds with adjusted predictions calculated by competing-risks regression models while adjusting by center and calendar year of patient recruitment.

Fig. 3. Influence of hepatic steatosis on liver-related outcomes in cirrhotic patients.

(A) Overall survival without transplant by steatosis and CTP score. Cox model adjusted probabilities. [a]

(B) Hepatic decompensation by steatosis and CTP score. Competing-risks adjusted cumulative incidences. [b]

(C) HCC development by steatosis and CTP score. Competing-risks adjusted cumulative incidences. [c]

[a] HR for CTP-A5 + steatosis < 33% = 3.9 (95% CI: 1.7-9.4), CTP-A6 + steatosis ≥ 33% = 10.8 (95% CI: 4.9-23.5) and CTP-A6 + steatosis < 33% = 18 (95% CI: 7-45.5). Cox model adjusted $P<0.05$ for difference among groups.

[b] sHR for CTP-A5 + steatosis < 33% = 4.4 (95% CI: 2.5-9.1), CTP-A6 + steatosis ≥ 33% = 12.1 (95% CI: 5.9-24.8) and CTP-A6 + steatosis < 33% = 12.8 (95% CI: 5.4-30.1). No statistically significant difference between CTP-A6 + steatosis ≥ 33% and CTP-A6 + steatosis < 33%.

[c] sHR for CTP-A5 + steatosis < 33% = 2.4 (95% CI: 1.01-5.5) and CTP-A6 + steatosis < 33% = 3.8 (95% CI: 1.6-8.7). No statistically significant difference among CTP-A5 and A6 with steatosis > 33%.

Cumulative probability or incidence curves for each outcome indicates adjusted predictions calculated by Cox or competing-risks regression models adjusted by center and calendar year of patient recruitment.

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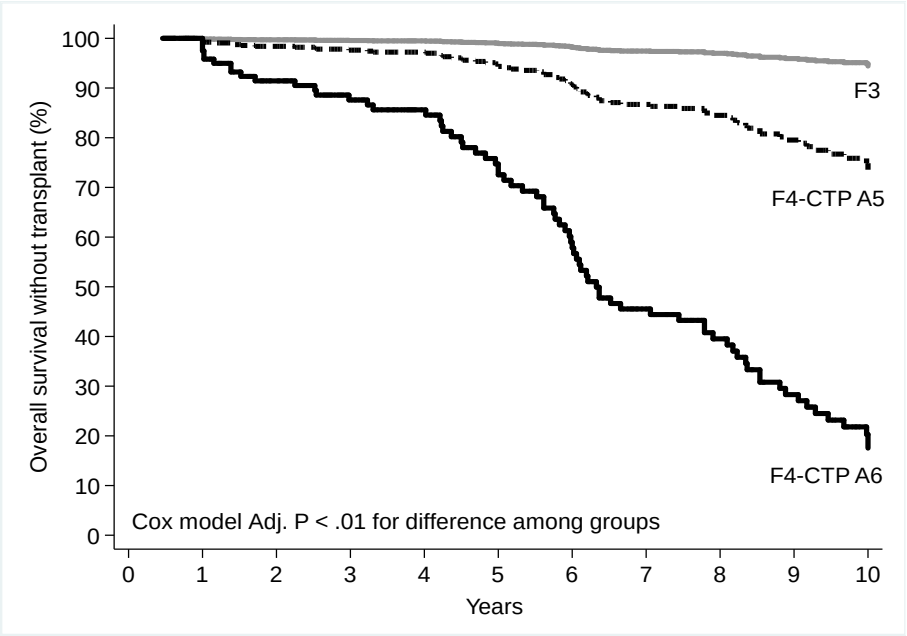
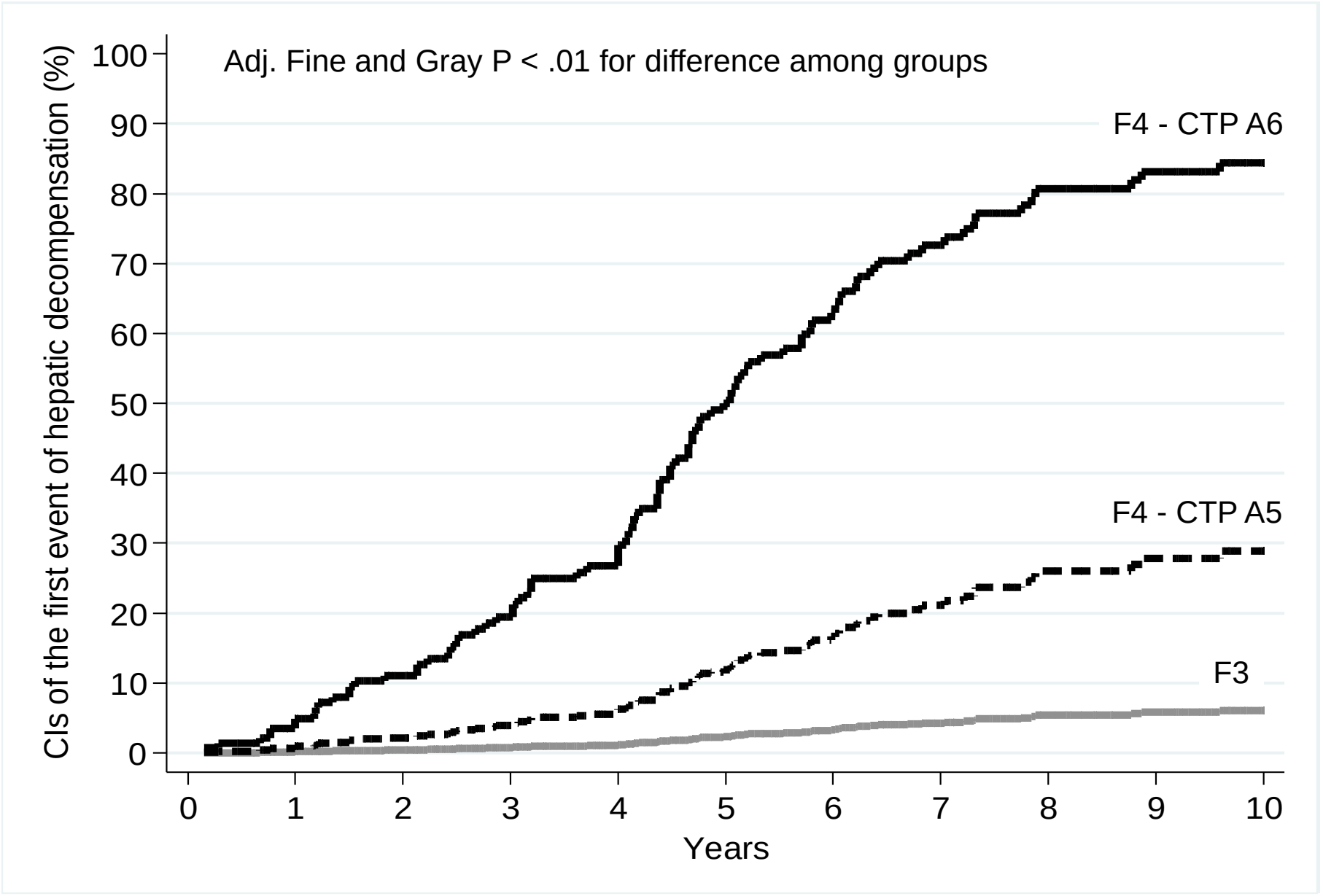


No. at risk											
F3	159	157	144	115	102	81	72	54	41	31	20
F4-CTP A5	222	212	191	155	129	112	96	77	63	56	43
F4-CTP A6	77	74	58	55	53	44	30	24	18	11	5



No. at risk

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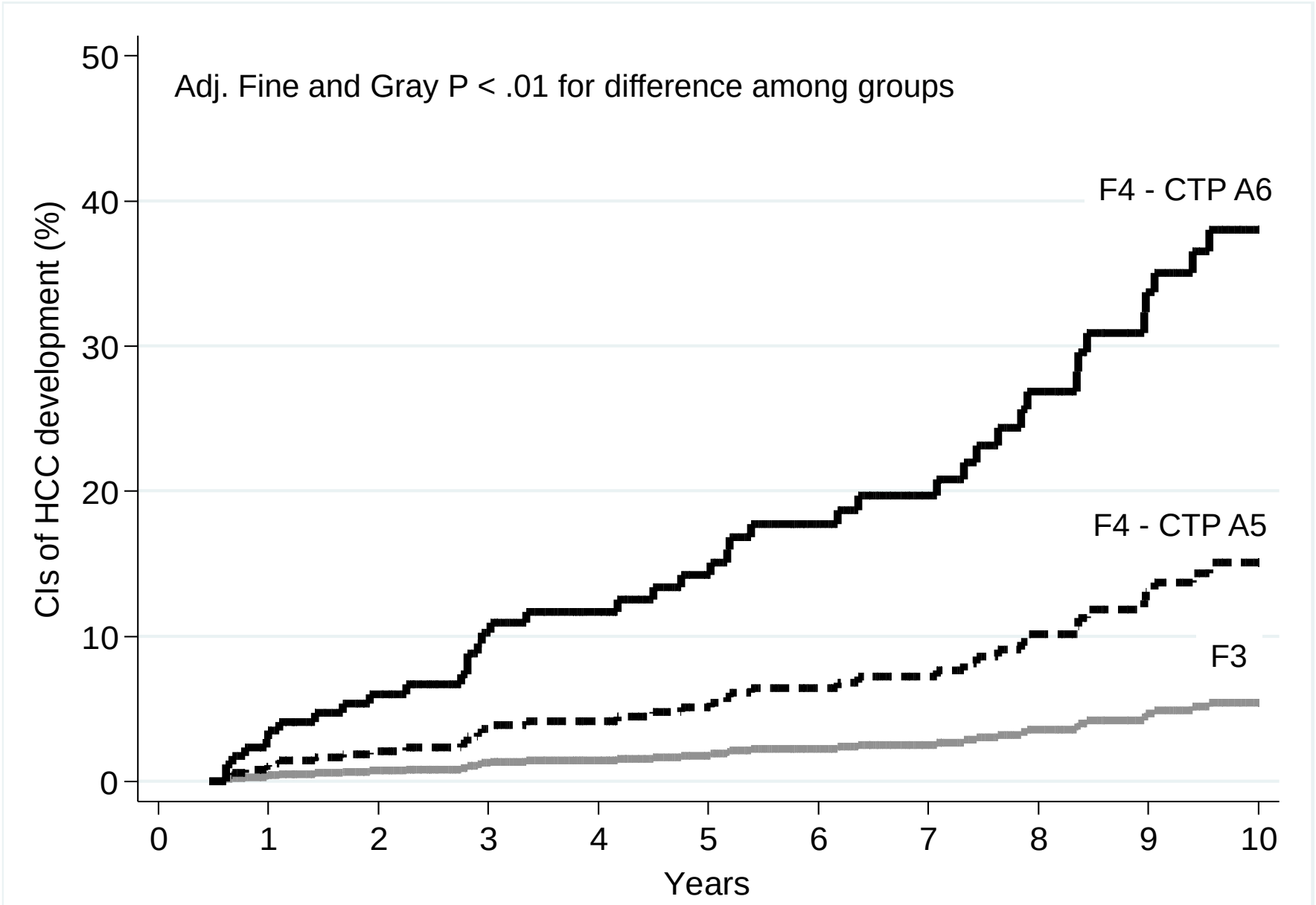
F4-CTP A6	77	72	55	43	35	23	12	7	4	4	2



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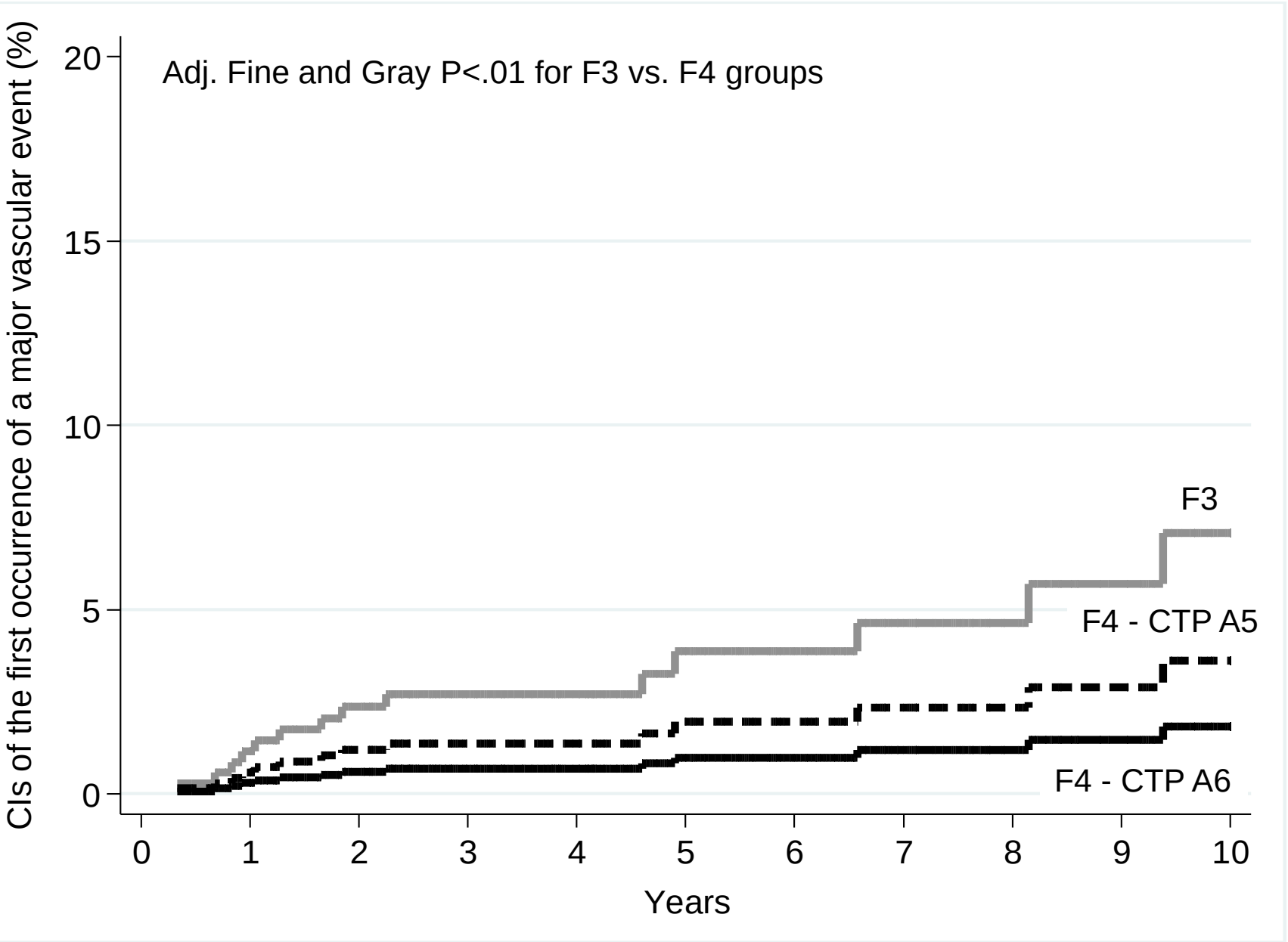
F4-CTP A6	77	72	57	53	50	40	27	20	15	9	4



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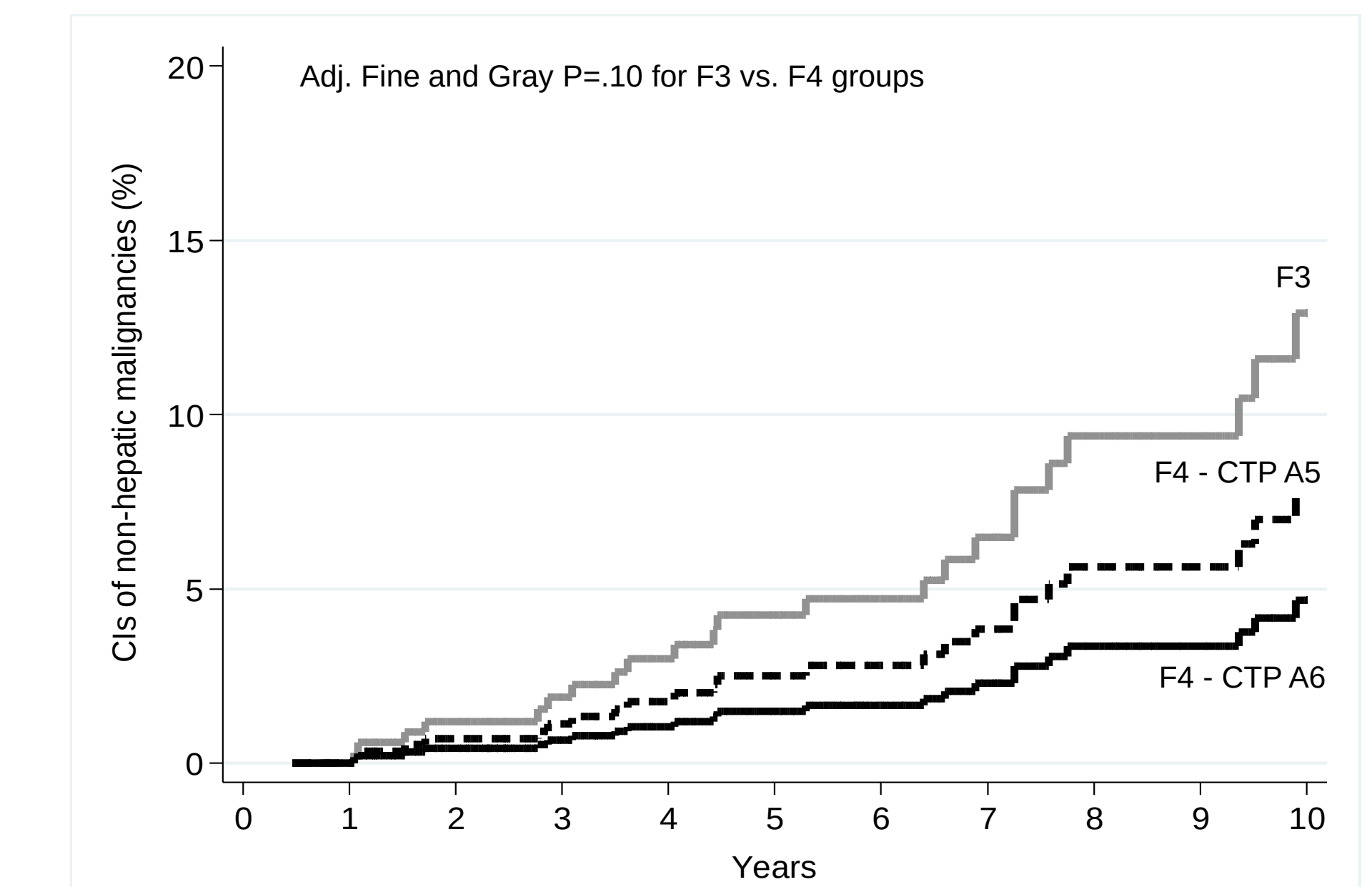
F4-CTP A6	77	74	58	55	53	44	30	23	17	10	5



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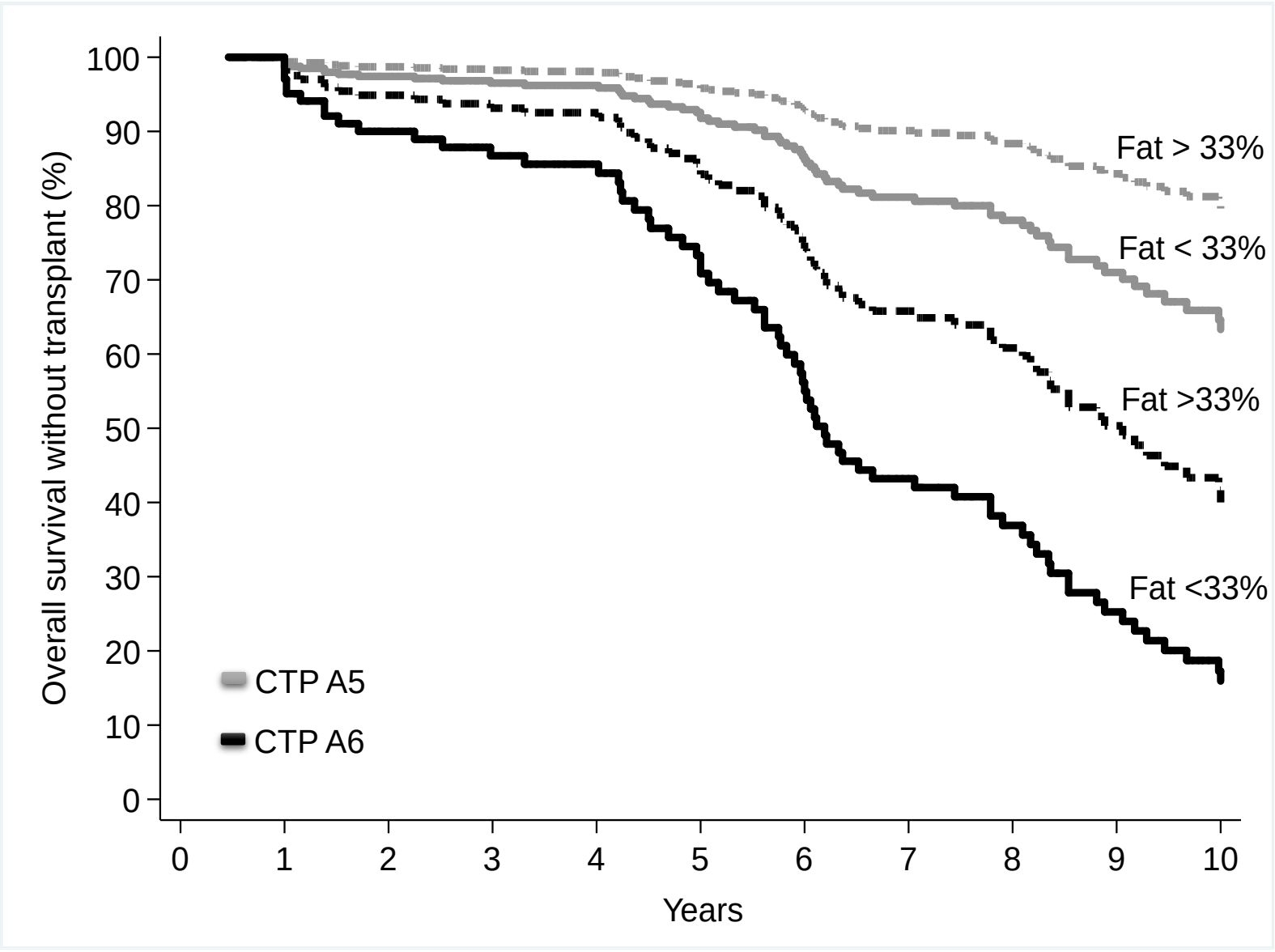
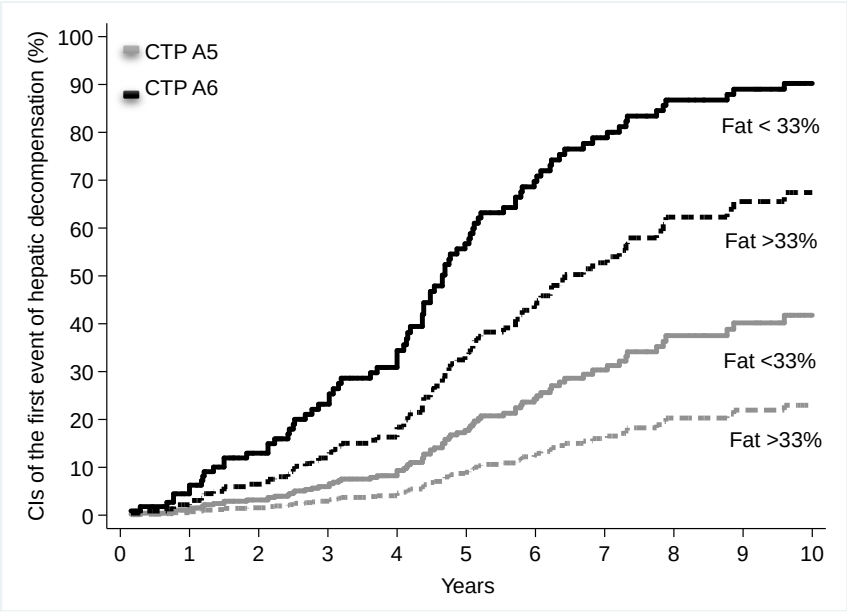
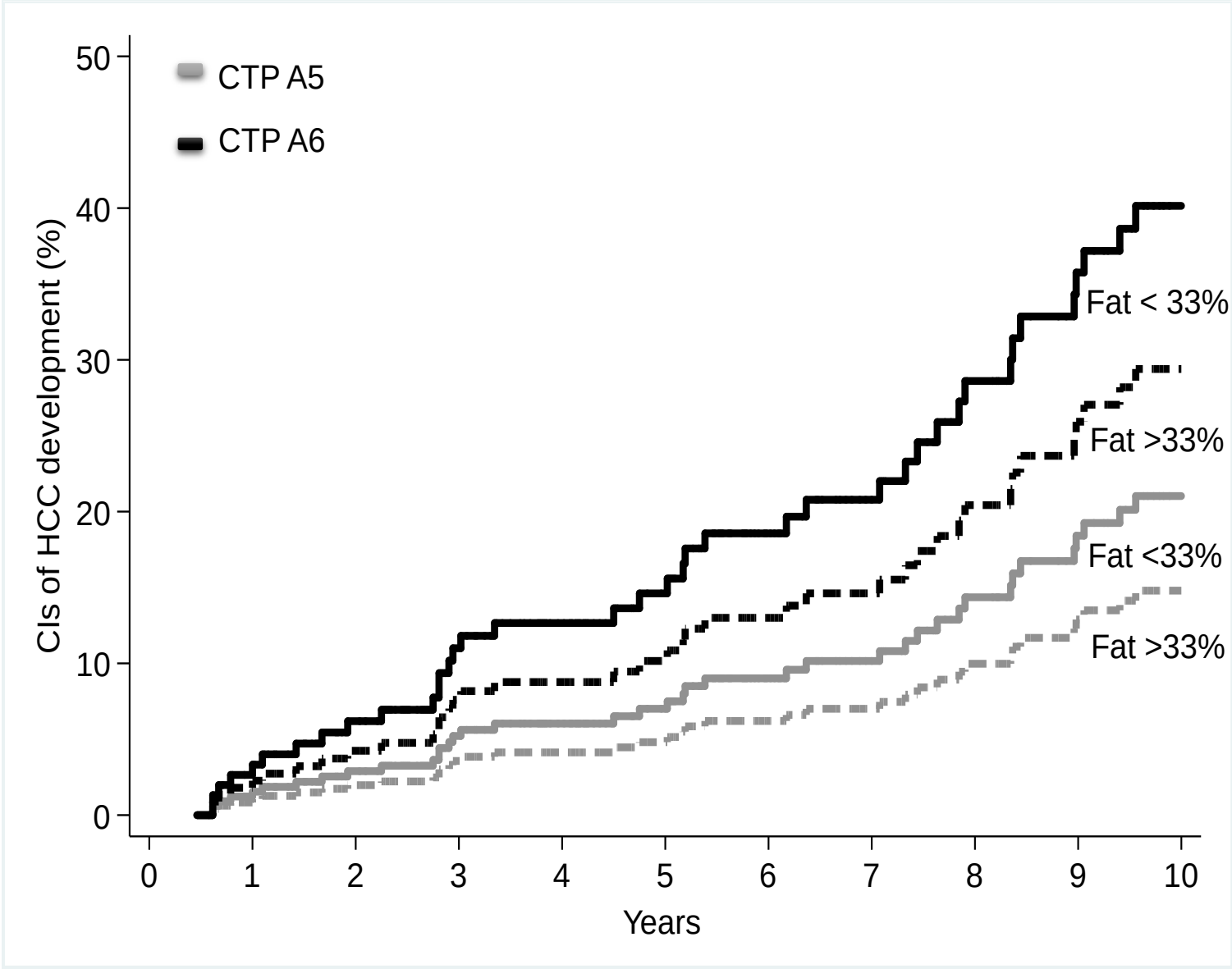


No. at risk

A5 + Fat > 33%	136	133	120	102	82	70	60	53	43	41	29
A5 + Fat < 33%	86	79	71	53	47	42	36	24	20	15	14
A6 + Fat > 33%	24	21	14	12	12	9	4	3	2	2	0
A6 + Fat < 33%	53	53	44	43	41	35	26	21	16	9	5



No. at risk											
A5 + Fat > 33%	136	133	120	102	81	62	52	44	36	35	24
A5 + Fat < 33%	86	76	65	51	45	36	29	21	13	8	6
A6 + Fat > 33%	24	19	12	9	9	6	3	2	1	1	0
A6 + Fat < 33%	53	53	43	34	26	17	9	5	3	3	2



No. at risk											
A5 + Fat > 33%	136	133	119	98	78	66	56	49	38	36	26
A5 + Fat < 33%	86	79	70	53	47	41	33	24	18	11	10
A6 + Fat > 33%	24	20	14	12	12	9	4	3	2	2	0
A6 + Fat < 33%	53	52	43	41	38	31	23	17	13	7	4

SUPPLEMENTARY APPENDIX

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METHODS

Data collection

All patients were enrolled and assessed by experienced hepatologists in each participating center. The demographic and clinical data included age, gender, race, body weight in kg, height, body mass index (BMI), history of comorbidities, including hypertension and type 2 diabetes, and concurrent medications, self-reported cigarette smoking in the two years preceding enrollment. History of cardiovascular, cerebrovascular, and peripheral arterial disease, and previous malignancies was recorded. Laboratory parameters, including aminotransferases, GGT, bilirubin, serum albumin and creatinine, INR, platelets, fasting glucose and insulin, hemoglobin A1c, serum total and HDL cholesterol, triglycerides, LDL cholesterol and alpha-fetoprotein were collected.

Alcohol use information was obtained via patient interview and confirmed by relatives at baseline and during follow-up visits. Patients were asked to describe their alcohol consumption during a typical week, changes during the last 2 years, as well as changes in alcohol consumption during each follow-up visit. Type (wine, beer, and liquor) and amount of beverages drunk during a week was considered for computing weekly alcohol intake. The amount of each beverage type was summed to obtain a total quantity, and an average daily quantity was calculated. A standard drink of wine was considered to contain 4 ounces, beer 12 ounces, and liquor 1.5 ounces of ethanol. To compute weekly alcohol intake during each clinic visit, the number of drinking episodes was multiplied by the number of drinks (in grams of ethanol) consumed on each episode. Subjects who reported two or more episodes of alcohol consumption over 140 g/week (men) and 70 g/week (women) were excluded. Alcohol consumption was classified into (1) non-drinkers: lack of alcohol intake or (2) moderate drinkers: between 1-70 g/week (women) and 1-140 g/week.

Body weight was measured on calibrated scales by clinical staff.

Type 2 diabetes was defined as fasting glucose $\geq$ 126 mg/dL or HbA1c $\geq$ 6.5 % or use of insulin or oral hypoglycemic medication. Fasting blood glucose or HbA1c or any newly prescribed antidiabetic medication on follow-up visits were used to detect new-onset diabetes among those subjects with diabetes at baseline. Hypertension was defined as systolic blood pressure >130/85 mmHg or taking antihypertensive medications.

Follow-up and events assessment

A comprehensive protocol including specifications on outcomes assessments was distributed and discussed among all participating centers, and 1 or 2 experienced local investigators confirmed and certified the occurrence and type of outcome based on protocol specifications. Finally, reported outcomes were re-assessed by 2 investigators (EVG and LCB) to assurance the quality of reports.

During the follow-up, patients with elevated AFP levels and/or new lesions suspected or detected during US examination were further evaluated with either triphasic computerized tomography (CT), contrast-enhanced magnetic resonance (MR) imaging, hepatic angiography and/or ultrasound-guided needle liver biopsy.

Upper digestive endoscopies were performed by each local center following recommended guidelines for the management of patients with cirrhosis.[1]
Clinical outcomes occurring after liver transplantation were not considered. Each clinical event was verified and confirmed by the local investigator after extensive review of the patient clinical history, examination findings and investigations. Diagnoses of liver- and nonliver-related clinical events such as ascites, variceal hemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis, HCC and cardiovascular/cerebrovascular were made according to standardized accepted criteria.[1-8] Diagnoses of non-hepatic cancers were verified using histopathology and/or cytology findings.
Information on body weight, alcohol consumption, smoking status and diabetes status were systematically collected in each follow-up visit.

Histological analysis

Liver histology was assessed using hematoxylin and eosin (H&E) stains in paraffin-embedded sections using standardized methods. Fibrosis was assessed using both Masson's trichrome and Sirius Red stains in paraffin-embedded sections using established methodology. The grade of individual pathological features of NAFLD was scored on H&E-stained tissue.

In order to provide reliable estimation of grading and staging, only those biopsy specimens with a length greater than 10 mm and containing more than six portal tracts were included for analysis.

Inter-rater agreements between local histopathological (6 raters) and central readings (1 rater*) in 48 randomly selected patients (23 patients with bridging fibrosis and 25 with cirrhosis).

Histological variables	Inter-rater agreements using *Kappa* statistics					
	HK N=10	Australia-WH N=10	Australia-SCGH N=9	Spain-VRUH N=7	Spain-VUH N=6	Cuba-NIG N=6
Fibrosis	1.0	0.80	0.89	1.0	0.84	0.85
Steatosis	0.85	0.81	0.83	0.72	0.71	0.75
Lobular inflammation	0.63	0.44	0.53	0.58	0.48	0.45
Ballooning	0.75	0.54	0.53	0.59	0.55	0.57

* The pathologist (A.C) participating in central readings was not involved in initial readings. He was unaware of initial pathological reports and study information.
Abbreviations: HK, Hong Kong; **WH**, Westmead Hospital; **SCGH**, Sir Charles Gairdner Hospital; **VRUH**, Virgen del Rocio University Hospital; **VUH**, Valladolid University Hospital; **NIG**, National Institute of Gastroenterology.

Statistical analysis

Non-liver deaths were considered as competing events for liver-related mortality and transplant, hepatic decompensation and HCC; non-vascular deaths and transplant for vascular events; and non-cancer deaths, HCC-deaths or transplant for non-hepatic malignant neoplasms.

The Fine and Gray model is based on the hazard of the subdistribution and provides a simple relationship between covariates and cumulative incidence. As in any other regression analysis, modelling cumulative incidence functions for competing risks can be easily used for identifying potential prognostic factors for a particular outcome in the presence of competing risks events, or to assess a prognostic factor of interest after adjusting for other potential risk factors in the model.

As an example, the standard Cox model, like to the standard Kaplan-Meier estimator, may introduce a bias in the estimates of absolute risk because it fails to treat subjects who die of non-liver related causes as ineligible for development of liver-related deaths or other liver-related events. Standard methods treat inadequately competing events as if they were censored. In competing risk analysis, subhazard ratios (sHR) can be interpreted similarly to hazard ratios (HR) in Cox regression models.

Covariates were selected for analysis according to their biologically plausible potential to act as confounders or predictors for each outcome. The potential predictors at baseline were as follows: age, gender, race/ethnicity, fibrosis stages (bridging fibrosis vs. cirrhosis) and CTP score classes (A5 and A6), total bilirubin, albumin, platelets, total cholesterol, INR, AST/ALT ratio, diabetes mellitus, individual histological lesions (lobular inflammation, steatosis and ballooning), gastroesophageal varices at baseline and MELD score. Smoking status, alcohol consumption and diagnosis of type 2 diabetes were considered as time-dependent covariates.

The diagnosis of new-onset diabetes over time among non-diabetic patients was systematically collected during each visit. The first follow-up contact at which there was new diabetes diagnosis was utilized to define conversion to diabetes during follow-up. In all analyses including incident diabetes, a time-varying covariate was generated by considering change in diabetes status over time. In other words, we considered patients in the non-diabetes group until they developed diabetes. Similarly, among non-smoking and non-drinkers patients, the first follow-up contact at which there was a new episode of smoking or alcohol intake was utilized to define conversion to smoking or drinkers during follow-up. Among smoking and drinker patients, the first follow-up contact at which patients became a non-drinker and non-smoking was utilized to define conversion to non-smoking or non-drinker during follow-up. In all analyses including smoking and alcohol intake, a time-varying covariate was generated by considering change in status of smoking or alcohol consumption over time.

All cumulative outcomes rates including transplant-free survival, and nonliver-related clinical events were adjusted by centers and calendar year of patients' recruitment. Patients with history of severe vascular diseases or malignant neoplasm and reduced life expectancy were excluded. In patients with pre-existing vascular disease, a new episode of vascular disease including myocardial infarction, coronary artery disease, stable and unstable angina, impairment of heart failure, cardiac arrest, stroke, carotid or aortic artery disease, and transient ischemic attacks was considered as a new event and it was

accounted for analysis. Follow-up time for vascular event start at enrollment and continued until the first diagnosis of a vascular event. Subjects with cancers and palliative care or oncology treatment at enrollment (including surgery, chemotherapy or radiotherapy) were excluded. We assumed a second primary malignancy as a new event, and relapse of the same malignancy was not accounted for analysis. Pre-existing history of vascular events or malignancy was included as a covariate in all multivariable analyses.

When the prognostic models (CTP and MELD scores) and their individual components were significant at univariate analysis, multivariable models included separately the single components and the scores to avoid redundancy. Similarly, fibrosis severity and steatosis grades were evaluated in independent models. The collinearity between factors included in the multivariable analyses was checked by using VIF (variance inflation factor) and tolerance (1/VIF) values. Variables with very high VIF values indicating possible redundancy entered into different multivariable models.

All multivariable analyses were also adjusted by center, race/ethnicity, calendar year of patients' recruitment, hypertension, anti-diabetic, antihypertensive and hypolipidemic drugs, aspirin, and history of previous vascular events or malignant neoplasm.

Variables that were significant ($p<0.15$) in univariate analysis and those known as weighted prognostic indicators were included in multivariable analysis. Backward stepwise selection method was implemented for variable selection in Cox proportional hazard and competing risks regression models.

All adjusted Cox and competing risk regression models were performed on the dataset containing imputed values. A graphical assessment of proportional assumptions was performed using log-log survival curves. In addition, deviations from the assumption of proportionality were tested for each covariate and also globally, using Schoenfeld residuals. The assumptions of proportionality were met both globally (the overall models) and individually for each predictor variable.

Proportion of missing data for potential predictors

Variables	Proportion of missing data
Clinical	
Smoking status	6%
Body weight	4%
Alcohol consumption	0%
Metabolic determinations	
Cholesterol	4%
Triglycerides	4%
HDL cholesterol	4%
LDL cholesterol	4%
HbA1c	6%
Fasting insulin/HOMA-IR	8%
Liver tests	
ALT	0%
AST	0%
Albumin	0%
INR	0%
Bilirubin	0%
Platelets	0%
GGT	1%
Other tests	0%
MELD	0%
Creatinine/eGFR	0%
Upper GI endoscopy*	0%

* All cirrhotic patients underwent varices screening at baseline.

Proportion of missing data during the follow-up for time-dependent predictors	
Smoking status	2%
Alcohol consumption	0%

We applied a method of multiple imputations by chained equation (MICE) in which missing data are imputed or replaced with a set of plausible values.[9-11] MICE is an interactive

imputation method that imputes multiple variables by using chained equations, a sequence of univariate imputations methods with fully conditional specifications of predictions equations. We included transplant-free survival as outcome and baseline or time-varying predictors including alcohol consumption, smoking, severity of fibrosis and liver disease, diabetes, age, gender, concurrent medications and all potential confounders in the imputation procedure. We did 20 imputations for each missing information.

RESULTS

The mean follow-up in years based on race/ethnicity was as follow: Non-Hispanic White, 4.2; Hispanic White, 6.2; Asian, 4.9 and Black, 8.2 (One-way ANOVA P=0.22). The mean follow-up was not different among patients with bridging fibrosis and cirrhosis with CP class A5 and A6 (**see supplementary Figure 1**).

As shown in **supplementary Table 2**, some key baseline characteristics were significantly different among countries. For instance, Hong Kong patients showed less severity of liver disease, as determined by some liver tests such as INR, albumin, total bilirubin and platelet, in comparison with the remaining countries, and this finding may explain the lower proportion of patients with CTP A6 among Hong Kong subjects. Since many comorbidities (e.g., diabetes, arterial hypertension) and liver- and non-liver-related blood tests (e.g., cholesterol, albumin, bilirubin, INR, etc.) may be influenced by the severity of liver disease, **supplementary Table 2** also shows adjusted analysis by fibrosis and CTP score. Interestingly, only BMI and waist circumference were statistically different among all countries after adjustments by severity of liver disease which suggest the differences in baseline characteristics were greatly influenced by the proportion of patients with cirrhosis and CTP A6 that were enrolled in each country (**see also Table 1**). Based on the previous analysis and considering that severity of fibrosis and CTP (A5 vs. A6) classes are related to study outcomes, all statistical analysis included adjustments by both variables.

Fifty-eight (13%) patients had an estimated glomerular filtration rate of <60 mL/min/1.73m^2 of whom 45 (78%) had cirrhosis. Five patients underwent dialysis or renal transplant during follow-up due to marked impairment of renal function.

Survival and clinical outcomes over time

A total of 74 deaths (37, 50%) or liver transplants (37, 50%) occurred; 141 (31%) patients developed at least a first major clinical event (86 [61%] hepatic

decompensations, 22 [16%] HCCs, 13 [9%] major vascular events and 20 [14%] non-hepatic malignancies) and 4 (1%) subjects were lost to follow-up.

Supplementary Figure 2 illustrates transplant-free survival in overall cohort after adjustments by center, calendar year of recruitment and baseline fibrosis.

Transplant-free survival was 88% (95% CI: 84-96), 75% (95% CI: 69-93) and 57% (95% CI: 49-64) at 5, 7 and 10 years follow up, respectively in cirrhotic patients. The **supplementary Figure 6** displays survival rates among patients with bridging fibrosis and compensated cirrhosis, including both CTP A5 and A6 in the same group.

Race/ethnicity as predictors of outcomes

Although Asian patients had better rates of survival and liver-related outcomes than remaining ethnic subgroups, these differences disappeared after adjustments by Child-Pugh score or other parameters related to severity of liver disease (INR, bilirubin, albumin or platelets). Only 2% of Asian patients had a CP score of 6 as compared to 16% and 22% of Hispanic- and non-Hispanic White subgroups (**see Table 1 and supplementary Figures 3 A-B**). There were too few Blacks to perform meaningful analyses of individual outcomes by this ethnic subgroup.

TABLES

Table 1. Distribution of biochemical components in patients with CTP class A6

Biochemical components CTP score	**Cut-off values**	**CPT-A6 n=77 N (%)**
Albumin (g/dl)	>3.5	47 (61)
	2.8-3.5	30 (39)
INR	<1.7	71 (92)
	1.7-2.2	6 (8)
Bilirubin (mg/dl)	< 2	61 (79)
	2-3	16 (21)

Patients with albumin <3.0 g/dL, total bilirubin > 3.0 mg/dL and INR >2 were excluded in our study.

Table 2. Key baseline characteristics by countries.

Variable	Spain n=184	Australia n=116	Hong Kong n=82	Cuba n=76	P value [c]	Ajd. P value [d]
Clinical						
Age (y)	54.4 ± 9.9	56.4 ± 12.4	56.9 ± 10.4	56.1 ± 10.6	0.08	0.19
Male, n (%)	97 (50)	53 (46)	43 (52)	25 (38)	0.44	0.37
Current smoking, n (%)	47 (24)	15 (13)	7 (9)	9 (12)	0.23	0.11
Alcohol consumption, n (%)						
Moderate drinkers	25 (13)	18 (16)	15 (18)	8 (12)	0.76	0.62
History of hypertension, n (%)	119 (61)	62 (53)	61 (74)	39 (59)	0.02	0.09
Type 2 diabetes, n (%)	117 (60)	80 (69)	66 (80)	42 (63)	0.08	0.20
BMI (kg/m^2)	34.7 ± 9.2	36.6 ± 8.9	28.5 ± 4.9	28.8 ± 4.4	<0.01	<0.01
Waist (cm)	109.8 ± 12.9	114.2 ± 16.7	97 ± 14.1	96.3 ± 13.1	<0.01	<0.01
History of vascular diseases, n (%)	14 (8)	14 (12)	6 (7)	5 (6)	0.15	0.17
10-y heart/stroke risk score [a]	12.3 ± 11.6	12.8 ± 12.9	13.9 ± 12.1	14.1 ± 12.7	0.28	0.23
Biochemical						
MELD score	7.8 ± 2.4	7.8 ± 2.9	7.2 ± 1.8	8.1 ± 2.8	0.05	0.15
ALT (U/L)	64.3 ± 43.4	64.8 ± 51.7	66.2 ± 36.3	68.3 ± 41.8	0.88	0.96
AST (U/L)	61.6 ± 37.5	54.5 ± 37.5	50.4 ± 27.9	75.9 ± 66.2	0.42	0.33
AST/ALT ratio	1.09 ± 0.52	0.95 ± 0.36	0.86 ± 0.35	1.25 ± 0.45	0.04	0.14
Total bilirubin (mg/dl)	0.78 ± 0.45	0.84 ± 0.74	0.65 ± 0.18	1.19 ± 0.65	<0.01	0.17
Albumin (g/dl)	4.07 ± 0.35	4.09 ± 0.42	4.44 ± 0.29	4.10 ± 0.49	<0.01	0.15
INR	1.09 ± 0.31	1.08 ± 0.20	1.02 ± 0.05	1.15 ± 0.36	<0.01	0.13
Platelets (x 10^9/L)	172 ± 56	196 ± 83	210 ± 72	167 ± 61	0.01	0.09
HbA1c (%)	7.32 ± 1.95	6.76 ± 1.82	7.15 ± 1.5	6 ± 1.92	<0.01	0.23
HOMA-IR	9.5 ± 6.9	8.7 ± 6.2	6.3 ± 5.4	6.1 ± 5.1	<0.01	0.08
Cholesterol (mg/dl)	198.4 ± 50.8	165.4 ± 48.2	170.3 ± 40.9	175.3 ± 61.6	<0.01	0.14
HDL cholesterol (mg/dl)	44.6 ± 10.8	43.8 ± 12.4	49.6 ± 14.4	40.2 ± 4.2	0.03	0.25
LDL cholesterol (mg/dl)	117.6 ± 44.9	90.4 ± 36.9	94.3 ± 38.4	105.4 ± 53	0.13	0.31
Triglycerides (mg/dl)	169.7 ± 87	152.1 ± 78.7	171 ± 119.7	183.3 ± 84.6	0.08	0.29
α-fetoprotein (ng/ml)	3.79 ± 1.92	3.46 ± 1.66	3.37 ± 1.76	3.71 ± 1.67	0.44	0.37
eGFR <60 mL/min/1.73m^2	18 (9)	19 (16)	11 (13)	10 (15)	0.16	0.52

Liver histology						
Biopsy length (mm)	19.2 ± 4.1	17.8 ± 5.5	19.4 ± 6.3	19.9 ± 4.7	0.15	0.16
Portal tracts (n)	10.9 ± 2.8	8.9 ± 2.5	8.3 ± 3.2	9.6 ± 2.2	0.08	0.06
NAS [b]	4.3 ± 1.6	4.2 ± 1.9	4.1 ± 1.2	4.1 ± 1.9	0.05	0.11
Steatosis	1.85 ± 0.80	1.60 ± 0.99	1.86 ± 0.74	1.68 ± 0.93	0.04	0.10
Lobular inflammation	1.41 ± 0.68	1.29 ± 0.61	1.37 ± 0.61	1.28 ± 0.80	0.01	0.08
Ballooning	1.18 ± 0.62	1.04 ± 0.49	1 ± 0.56	0.96 ± 0.71	<0.01	0.13

Abbreviations: **MELD**, Model for End-Stage Liver Disease; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **HbA1c**, glycated hemoglobin; **HOMA-IR**, Homeostatic Model Assessment of Insulin Resistance; **HDL**, high-density lipoprotein; **LDL**, low-density lipoprotein; **INR**, international normalized ratio; **eGFR**, estimated glomerular filtration rate; **NAS**, NAFLD activity score.

Quantitative data were expressed as mean ± SD.

The eGFR was computed by EPI-CKD formula.

Vascular diseases include cardiovascular, cerebrovascular and peripheral vascular diseases.

[a] The 10-year risk of heart disease or stroke using the ASCVD algorithm published in 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.[12]

[b] NAS indicates NAFLD activity score. It was defined as the unweighted sum of the scores for steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2); thus, ranging from 0 to 8.

[c] For continuous variables, one-way analysis of covariance (ANCOVA) with Bonferroni adjustments for multiple comparisons (P<0.01). For qualitative variables, Mantel-Haenszel chi-square test for trend.

[d] Adjusted analysis by fibrosis severity and CTP score at baseline.

Table 3. Clinical outcomes during the follow-up.

Clinical outcomes	Overall n=458 N
Overall mortality and liver transplant	74
Deaths	37
Liver-related	31
Hepatorenal syndrome	7
HCC	6
Spontaneous bacterial peritonitis	3
Hepatic encephalopathy	4
Variceal bleeding	2
Systemic sepsis	4
Acute on chronic liver failure	2
Liver failure	2
Cholangiocarcinoma	1
Non liver-related	6
Cardiac arrest	1
Lung cancer	1
Aortic abdominal aneurysm rupture	1
Myocardial infarction	1
Colorectal cancer	2
Liver transplantation	37
Hepatic decompensation	26
Hepatocellular carcinoma	6
End-stage kidney disease [a]	5
First events of hepatic decompensation	90
Ascites	63
Variceal hemorrhage	22
Hepatic encephalopathy	5
Hepatocellular carcinoma	41
Major vascular events	14
Heart ischemic disease	10

Stroke (ischemic)	4
Non-hepatic malignant neoplasm	30
Colorectal cancer	15
Skin cancer	6
Breast cancer	3
Uterine cancer	2
Esophageal cancer	1
Lung cancer	1
Pancreatic cancer	1
Cholangiocarcinoma	1

[a] Five patients underwent double kidney-liver transplantation.

Table 4. Variables found as significant predictors of overall mortality or transplant, hepatic decompensation and hepatocellular carcinoma. Results based on univariate Cox or competing-risks regression models.

Variable	**Overall mortality/liver transplant** [a] n=74		**Hepatic decompensation** [b] n=88		**Hepatocellular carcinoma** [b] n=41	
	Univariate		Univariate		Univariate	
	HR	*P*	*sHR*	*P*	*sHR*	*P*
Cirrhosis (yes)	9.12	<0.01	10.43	<0.01	9.67	<0.01
Race/ethnicity						
Asian	Ref	-	Ref	-	Ref	-
Non-Hispanic White	3.72	0.02	3.98	<0.01	10.06	0.03
Hispanic White	3.23	0.02	6.05	<0.01	5.63	0.06
Age, y	1.03	0.02	0.99	0.43	1.04	0.02
Gender (male)	1.27	0.30	0.93	0.75	6.11	<0.01
Varices (yes)	2.37	<0.01	3.22	<0.01	1.77	0.05
Current smoking (yes) [c]	1.6	0.04	2.2	<0.01	2.1	0.01
BMI (kg/m^2)	0.98	0.29	0.97	0.20	0.99	0.73
Hypertension (yes)	0.69	0.12	0.86	0.49	1.47	0.25
Type 2 diabetes (yes) [c]	2.14	<0.01	1.89	0.01	2.91	0.01
Cholesterol (mg/dl)	0.99	<0.01	0.99	0.05	1.01	0.61
Statin therapy (yes)	0.74	0.27	0.68	0.10	0.61	0.20
INR	10.33	<0.01	7.24	<0.01	2.54	0.02
Albumin (g/dl)	0.32	<0.01	0.26	<0.01	0.44	<0.01
Total bilirubin (mg/dl)	1.76	<0.01	1.41	<0.01	1.52	<0.01
AST/ALT	2.89	<0.01	2.69	<0.01	1.27	0.29
Platelets (x 10^9/L)	0.98	<0.01	0.98	<0.01	0.99	<0.01
MELD	1.14	<0.01	1.09	<0.01	1.06	0.22
CTP score						
F3	Ref	-	Ref	-	Ref	-
A5	4.22	<0.01	5.62	<0.01	7.28	<0.01
A6	25.12	<0.01	30.43	<0.01	15.47	<0.01
Steatosis < 33%	4.46	<0.01	4.7	<0.01	3.26	<0.01

Abbreviations: **CTP**, Child-Turcotte-Pugh; **sHR**, subhazard ratios; **BMI**, body mass index; **MELD**, Model for End-Stage Liver Disease; **INR**, international normalized ratio; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase.

The CTP and MELD scores are measures of the severity of liver disease.

[a] Univariate Cox regression models.

[b] Univariate competing risk regression models.

[c] Included as a time-dependent covariate.

Table 5. Influence of alcohol consumption on clinical outcomes. Cox or competing-risks regression models included alcohol consumption as a time-varying covariate.

	Bridging fibrosis n=159		**P Value** [a]	**Cirrhosis** n=299		**P Value** [a]	**Cirrhosis** N=299	
	Moderate consumption N (%)			*Moderate consumption N (%)*			*Adjusted HR or sHR (95% CI) for moderate consumption*	**P value** [b]
Death or transplant	*No*	*Yes*	*0.48*	*No*	*Yes*	*<0.01*	2.3 (1.32-4.02)	*<0.01*
No	140 (97)	15 (100)		209 (81)	20 (20)			
Yes	4 (3)	0 (0)		50 (19)	20 (50)			
HCC development			*0.15*			*<0.01*	3.22 (1.64-6.32)	*<0.01*
No	143 (99)	14 (93)		233 (90)	27 (67)			
Yes	1 (1)	1 (7)		26 (10)	13 (33)			
Hepatic decompensation			*0.43*			*<0.01*	1.65 (1.01-2.61)	*0.04*
No	142 (91)	15 (100)		212 (72)	21 (52)			
Yes	2 (1)	0 (0)		47 (18)	19 (48)			
Vascular events			*0.31*			*0.56*	-	-
No	136 (94)	15 (100)		253 (98)	40 (100)			
Yes	8 (6)	0 (0)		6 (2)	0 (0)		-	-
Non-hepatic malignancies			*0.62*			*0.77*		

No	135 (94)	14 (97)	247 (95)	39 (97)	-	-
Yes	9 (6)	1 (3)	12 (5)	1 (3)	-	-

[a] Unadjusted P values.

[b] P values after adjustments by those variables that were significant at univariate analysis (**supplementary appendix, Table 4**) and centers, race/ethnicity, calendar year of patients' recruitment, baseline BMI, diabetes, hypertension, anti-diabetic, antihypertensive and hypolipidemic drugs, aspirin, and history of previous vascular events or malignant neoplasm.

Table 6. Influence of individual histological lesions on overall mortality or transplant and hepatic outcomes. Results based on Cox or competing-risks regression models.

Histological lesion	**Overall mortality/OLT [a]** n=74				**Hepatic decompensation [b]** n=88				**Hepatocellular carcinoma [b]** n=41			
	Unadjusted		*Adjusted [c]*		*Unadjusted*		*Adjusted [c]*		*Unadjusted*		*Adjusted [d]*	
	HR	*P*	*HR*	*P*	*sHR*	*P*	*sHR*	*P*	*sHR*	*P*	*sHR*	*P*
Steatosis												
< 33%	2.67	<.01	2.50	<.01	2.97	<.01	2.91	<.01	3.53	.01	3.52	.01
Ballooning												
None or few cells	1.74	.09	1.68	.11	1.11	.41	1.06	.82	1.14	.72	1.11	.78
Lobular inflammation												
None or < 2 foci per 200x field	1.25	.23	1.20	.33	1.09	.61	1.05	.77	1.21	.46	1.29	.30

Cox [a] and competing-risks [b] regression models.

[c] Adjusted analyses include centers and calendar year of patients' recruitment, age, sex, race/ethnicity, CTP classes, diabetes, alcohol consumption and baseline BMI.

Table 7. Variables found predictors of vascular events. Results based on multivariable competing-risks regression models.

Variable	**Major vascular events (n=14)**		
	Multivariable		
	sHR	*95% CI*	*P*
Cirrhosis (yes) [a]	0.25	0.08-0.71	<0.01
Age, y	1.05	1.01-1.13	0.04
BMI (kg/m^2)	1.07	1.02-1.17	0.03
Type 2 diabetes (yes) [b]	2.15	1.14-7.96	0.02
LDL cholesterol (mg/dl)	1.06	1.02-1.15	0.02

[a] No difference was detected between CTP A5 and A6.

[b] Included as a time-dependent covariate.

Table 8. Baseline features based on severity of steatosis.

Variable	Severity of steatosis		
	Steatosis < 33% n=181	Steatosis ≥ 33% n=277	*P* [a]
Age, y	57.8 ± 11.5	54.7 ± 10.9	<.01
Male (yes), n (%)	78 (43)	140 (51)	.12
BMI (kg/m^2)	31.6 ± 7.4	34.2 ± 9.1	<.01
Type 2 diabetes (yes), n (%)	127 (70)	178 (64)	.19
HbA1c (%)	6.97 ± 1.99	6.95 ± 1.82	0.84
LDL cholesterol (mg/dl)	98.7 ± 44.3	108.7 ± 44.6	.01
Triglycerides (mg/dl)	152.3 ± 74.5	177.3 ± 88.3	.01
Albumin (mg/dl)	4.06 ± 0.44	4.22 ± 0.37	<.01
INR	1.10 ± 0.17	1.05 ± 0.19	<.01
AST/ALT ratio	1.15 ± 0.47	0.96 ± 0.44	<.01
Platelets (x 10^9/L)	162 ± 69	198 ± 65	<.01
Total bilirubin (mg/dl)	1.02 ± 0.4	0.72 ± 0.28	<.01

[a] Wilcoxon signed-rank test for continuous variables and Chi square test for categorical variables.

Table 9. Outcomes development based on gender. Adjusted P values based on Cox or competing-risk regression models.

Variable	Gender		
	Male n=218	Female n=240	*P* [a]
Mortality or transplant	40 (18%)	34 (14%)	0.04
Liver-related decompensation	39 (18%)	49 (20%)	0.52
HCC	34 (16%)	7 (3%)	<0.01
Vascular events	7 (3%)	7 (3%)	0.78
Non-hepatic malignancies	9 (4%)	14 (6%)	0.41

[a] Adjusted Cox-model or Fine and Gray P values by centers, race/ethnicity, age, calendar year of patients' recruitment, smoking status, alcohol intake, baseline BMI, hypertension, anti-diabetic, antihypertensive and hypolipidemic drugs, aspirin, and history of previous vascular events or malignant neoplasm.

Table 10. Outcomes development considering type 2 diabetes diagnosis as a time varying covariate. Adjusted P values based on Cox or competing-risk regression models.

Variable	Diagnosis of type 2 diabetes		
	No n=132	Yes n=326	*P* [a]
Overall mortality or transplant	13 (10%)	61 (19%)	<0.01
Liver-related decompensation	19 (14%)	69 (21%)	<0.01
HCC	3 (2%)	38 (12%)	<0.01
Vascular events	1 (1%)	13 (4%)	0.01
Non-hepatic malignancies	7 (5%)	16 (5%)	0.87

[a] Adjusted P values by center, race/ethnicity, age, gender, calendar year of patients' recruitment, smoking status, alcohol intake, baseline BMI, hypertension, anti-diabetic, antihypertensive and hypolipidemic drugs, aspirin, and history of previous vascular events or malignant neoplasm.

Table 11. Association between **severity of fibrosis (model 1 in Table 4 of main manuscript)** and overall mortality or transplant, hepatic decompensation and hepatocellular carcinoma. Cox or competing risk regression multivariable analyses including other potential confounding or predictive factors.

Variable	**Overall mortality/liver transplant** [a] n=74		**Hepatic decompensation** [b] n=88		**Hepatocellular carcinoma** [b] n=41	
	Multivariable		Multivariable		Multivariable	
	HR (95% CI)	*P*	*sHR (95% CI)*	*P*	*sHR (95% CI)*	*P*
Cirrhosis (yes)	**5.99 (2.12-16.9)**	**<.01**	**6.55 (2.53-16.96)**	**<.01**	**6.52 (1.38-30.8)**	**<.01**
Race/ethnicity						
Asian	Ref	-	Ref	-	Ref	-
Non-Hispanic White	2.65	.13	2.23	.29	3.11	.08
Hispanic White	2.84	.11	2.53	.17	4.22	.10
Age, y	1.03 (1.01-1.06)	.01	0.98	.22	1.04 (1.01-1.08)	.03
Gender (male)	1.71 (1.0-2.67)	.05	1.11	.27	8.36 (2.75-24.4)	<.01
Current smoking (yes) [c]	1.69 (1.02-2.87)	.04	1.22	.40	3.18 (1.35-7.52)	<.01
Type 2 diabetes (yes) [c]	2.99 (1.55-5.88)	<.01	2.44 (1.33-4.99)	<.01	5.92 (1.86-18.8)	<.01
BMI (kg/m^2)	0.97	.17	0.97	.27	0.98	.91
Hypertension (yes)	0.82	.56	0.85	.66	0.68	.42
History of vascular events (yes)	0.66	.32	0.92	.86	0.88	.85

History of malignant neoplasm (yes)	1.44	.54	0.88	.87	0.92	.56
Statin therapy (yes)	1.19	.58	0.73	.25	0.66	.43
Glucose-lowering medications (yes)	0.59	.15	0.56	.11	0.78	.51
Anti-hypertensive medications (yes)	0.66	.29	1.36	.40	0.73	.52
Aspirin (yes)	0.57	.24	0.78	.69	0.52	.38

Abbreviations: HR, hazard ratio; **sHR**, subhazard ratios; **BMI**, body mass index.

All multivariable analyses were adjusted by centers and calendar year of patients' recruitment.

[a] Cox regression models.

[b] Competing risk regression models.

[c] Included as time-dependent covariate.

Table 12. Association between **CTP score (model 2 in Table 4 of main manuscript)** and overall mortality or transplant, hepatic decompensation and hepatocellular carcinoma. Cox or competing risk regression multivariable analyses including other potential confounding or predictive factors.

Variable	**Overall mortality/liver transplant** [a] n=74		**Hepatic decompensation** [b] n=88		**Hepatocellular carcinoma** [b] n=41	
	Multivariable		Multivariable		Multivariable	
	HR (95% CI)	*P*	*sHR (95% CI)*	*P*	*sHR (95% CI)*	*P*
Bridging fibrosis	Ref		Ref		Ref	
CTP A5	**3.83 (1.30-11.23)**	**<.01**	**4.47 (1.76-12.79)**	**<.01**	**6.7 (1.4-32.07)**	**<.01**
CTP A6	**21.26 (6.98-64.8)**	**<.01**	**19.42 (7.03-53.67)**	**<.01**	**8.15 (1.57-42.09)**	**<.01**
Race/ethnicity						
Asian	Ref	-	Ref	-	Ref	-
Non-Hispanic White	1.68	.41	1.26	.45	2.85	.35
Hispanic White	2.28	.14	2.7	.14	3.77	.18
Age, y	1.04 (1.01-1.07)	.01	0.98	.19	1.06 (1.01-1.11)	.01
Gender (male)	1.99 (1.01-3.08)	.03	0.86	.53	7.31 (2.48-21.5)	<.01
Current smoking (yes) [c]	1.75 (1.01-2.91)	.04	1.34	.19	2.42 (1.10-5.33)	.02
Type 2 diabetes (yes) [c]	2.78 (1.39-5.25)	<.01	2.44 (1.33-4.99)	<.01	5.92 (1.86-18.8)	<.01
BMI (kg/m^2)	0.99	.60	0.99	.96	0.99	.93

Hypertension (yes)	0.70	.31	0.89	.73	1.02	.55
History of vascular events (yes)	0.54	.28	0.72	.59	0.58	.28
History of malignant neoplasm (yes)	1.61	.49	1.16	.85	1.05	.37
Statin therapy (yes)	1.57	.15	0.88	.63	0.70	.44
Glucose-lowering medications (yes)	0.48	.11	0.61	.13	0.61	.39
Anti-hypertensive medications (yes)	0.66	.26	1.37	.33	0.60	.39
Aspirin (yes)	0.61	.28	0.81	.73	0.68	.45

Abbreviations: HR, hazard ratio; **sHR**, subhazard ratios; **CTP**, Child-Turcotte-Pugh; **BMI**, body mass index.

All multivariable analyses were adjusted by centers and calendar year of patients' recruitment.

[a] Cox regression models.

[b] Competing risk regression models.

[c] Included as time-dependent covariate.

Table 13. Association between **steatosis < 33% (model 3 in Table 4 of main manuscript)** and overall mortality or transplant, hepatic decompensation and hepatocellular carcinoma. Cox or competing risk regression multivariable analyses including other potential confounding or predictive factors.

Variable	**Overall mortality/liver transplant** [a] n=74		**Hepatic decompensation** [b] n=88		**Hepatocellular carcinoma** [b] n=41	
	Multivariable		Multivariable		Multivariable	
	HR (95% CI)	*P*	*sHR (95% CI)*	*P*	*sHR (95% CI)*	*P*
Steatosis < 33%	**2.56 (1.35-4.82)**	**<.01**	**2.64 (1.39-5.03)**	**<.01**	**2.21 (1.14-3.79)**	**<.01**
Race/ethnicity						
Asian	Ref	-	Ref	-	Ref	-
Non-Hispanic White	1.71	.39	2.30	.25	2.64	.38
Hispanic White	2.13	.16	2.76	.12	3.35	.20
Age, y	1.04 (1.01-1.06)	.02	0.98	.11	1.05 (1.01-1.10)	.02
Gender (male)	1.87 (1.01-2.87)	.04	0.77	.33	8.73 (3.06-24.9)	<.01
Current smoking (yes) [c]	1.80 (1.02-2.95)	.04	1.34	.19	2.71 (1.12-6.56)	.02
Type 2 diabetes (yes) [c]	2.84 (1.41-5.44)	<.01	3.19 (1.37-7.44)	<.01	8.59 (3.02-24.4)	<.01
BMI (kg/m^2)	0.99	.92	0.98	.44	0.98	.64
Hypertension (yes)	0.69	.30	0.73	.34	1.12	.79
History of vascular events (yes)	0.66	.33	0.69	.48	0.65	.37

History of malignant neoplasm (yes)	1.48	.55	1.08	.87	1.02	.41
Statin therapy (yes)	1.32	.39	0.69	.22	0.76	.60
Glucose-lowering medications (yes)	0.56	.13	0.77	.47	0.74	.45
Anti-hypertensive medications (yes)	0.63	.22	1.33	.37	0.66	.44
Aspirin (yes)	0.64	.31	0.77	.69	0.72	.51
INR	8.21 (3.33-17.9)	<.01	11.5 (5.66-28.5)	<.01	1.67	.42
Albumin (g/dl)	0.47 (0.26-0.85)	.01	0.31 (0.16-0.59)	<.01	0.73	.39
Total bilirubin (mg/dl)	1.93 (1.43-2.61)	<.01	1.44 (1.17-1.77)	<.01	1.58	.06
AST/ALT	2.85 (1.50-5.4)	<.01	2.38 (1.59-3.58)	<.01	1.20	.58
Platelets (x 10^9/L)	0.98 (0.98-0.99)	<.01	0.98 (0.98-0.99)	<.01	0.99	.33

Abbreviations: sHR, subhazard ratios; **BMI**, body mass index; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **INR**, international normalized ratio.

All multivariable analyses were adjusted by centers and calendar year of patients' recruitment.

[a] Cox regression models.

[b] Competing risk regression models.

[c] Included as time-dependent covariate.

Since all liver-related tests may reflect severity of liver disease and important collinearity (high VIF) was found between them, each variable (INR, albumin, total bilirubin, platelets count and AST/ALT ratio) was evaluated on independent models.

Table 14. Association between **other potential predictors (model 4 in Table 4 of main manuscript)** and overall mortality or transplant, hepatic decompensation and hepatocellular carcinoma. Cox or competing risk regression multivariable analyses.

Variable	**Overall mortality/liver transplant** [a] n=74		**Hepatic decompensation** [b] n=88		**Hepatocellular carcinoma** [b] n=41	
	Multivariable		Multivariable		Multivariable	
	HR (95% CI)	*P*	*sHR (95% CI)*	*P*	*sHR (95% CI)*	*P*
Cirrhosis (yes)	6.34 (2.23-18.03)	<.01	6.57 (2.47-17.46)	<.01	6.55 (1.40-31.3)	<.01
Gender (male)	1.87 (1.08-2.85)	.04	1.09	0.29	7.28 (3.1-17.1)	<.01
Race/ethnicity						
Asian	Ref	-	Ref	-	Ref	-
Non-Hispanic White	2.65	.13	2.20	.30	3.14	.07
Hispanic White	2.86	.10	2.55	.16	4.13	.11
Age, y	1.03 (1.01-1.06)	.01	0.98	.21	1.05 (1.01-1.10)	.01
GE varices (yes)	2.19 (1.13-3.71)	<.01	1.99 (1.16-3.05)	.01	-	-
Current smoking (yes) [c]	1.74 (1.03-2.98)	.03	1.22	.39	2.11 (1.17-5.27)	.01
Type 2 diabetes (yes) [c]	3.33 (1.69-6.54)	<.01	2.82 (1.54-5.15)	<.01	4.72 (2.13-10.45)	<.01
BMI (kg/m^2)	0.98	.40	0.97	.26	0.99	.82
Hypertension (yes)	0.73	.39	0.85	.64	0.71	.43

History of vascular events (yes)	0.68	.34	0.91	.85	0.77	.69
History of malignant neoplasm (yes)	1.40	.58	0.88	.87	0.91	.64
Statin therapy (yes)	0.95	.89	0.73	.25	0.57	.20
Glucose-lowering medications (yes)	0.68	.29	0.56	.12	0.74	.46
Anti-hypertensive medications (yes)	0.65	.27	1.35	.40	0.66	.49
Aspirin (yes)	0.54	.21	0.77	.70	0.58	.45
INR	7.19 (3.09-16.7)	<.01	4.34 (1.41-13.33)	.01	1.58	.58
Albumin (g/dl)	0.56 (0.30-0.91)	.05	0.47 (0.26-0.88)	.01	0.61	.23
Total bilirubin (mg/dl)	1.62 (1.19-2.21)	<.01	1.7 (1.4-2.1)	<.01	1.45	.26
AST/ALT	1.86 (1.12-3.09)	.01	1.56 (1.03-2.98)	.03	1.84	.14
Platelets (x 10^9/L)	0.99 (0.98-0.99)	.02	0.98 (0.97-0.99)	.01	0.99	.36
MELD score	1.10 (1.02-1.18)	<.01	0.99	.54	0.96	.46

Abbreviations: **CTP**, Child-Turcotte-Pugh; **sHR**, subhazard ratios; **BMI**, body mass index; **MELD**, Model for End-Stage Liver Disease; **INR**, international normalized ratio; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **GE**, gastroesophageal.

Since all liver-related tests may reflect severity of liver disease, and important collinearity (high VIF) was found between them, each variable (INR, albumin, total bilirubin, platelets count and AST/ALT ratio) was evaluated on independent models. Likewise, MELD score and their individual components were included separately in different models to avoid redundancy.

[a] Multivariable Cox regression models.

[b] Multivariable competing risk regression models.

[c] Included as a time-dependent covariate.

FIGURE LEGENDS

Fig. 1. Flow of patients through the study.

Fig. 2. Cox-model adjusted overall survival without transplant in the full cohort. [a]

[a] Survival curves represent adjusted predictions calculated by the Cox proportional regression model adjusted by centers, calendar year of patient recruitment and baseline fibrosis.

Fig. 3A. Cox-model adjusted overall survival without transplant according to races/ethnicities. [a]

[a] Survival curves represent adjusted predictions calculated by the Cox proportional regression model and adjusted by center, calendar year of patient recruitment and baseline fibrosis.

Spanish and Cuban people were represented as Hispanic Whites.

Fig. 3B. Cox-model adjusted overall survival without transplant according to races/ethnicities. [b]

[b] Survival curves represent adjusted predictions calculated by the Cox proportional regression model adjusted by center, calendar year of patient recruitment, baseline fibrosis and CTP score.

Spanish and Cuban people were represented as Hispanic Whites.

Fig. 4. Competing-risks adjusted cumulative incidence of a first major clinical event. [a]

[a] Outcome curves represent adjusted predictions calculated by the competing-risk regression model adjusted by center and calendar year of patient recruitment.

This outcome accounted for the first occurrence of a major clinical event (hepatic decompensation, HCC, vascular and non-hepatic malignancies) over time.

Fig. 5. Association between alcohol intake[a] and outcomes in cirrhotic patients.

(A) Cox-model adjusted overall survival without transplant. [b]

[b] Survival curves represent adjusted predictions calculated by the Cox proportional regression model adjusted by center and calendar year of patient recruitment.

(B) Competing-risks adjusted cumulative incidence of HCC development. [c]

[c] Cumulative incidences of HCC represent adjusted predictions calculated by the competing-risk regression model adjusted by center and calendar year of patient recruitment.

(C) Competing-risks cumulative incidence of the first hepatic decompensation. [d]

[d] Cumulative incidences of hepatic decompensation represent adjusted predictions calculated by the competing-risk regression model adjusted by center and calendar year of patient recruitment.

[a] Alcohol intake was analyzed as a time-varying covariate.

Fig. 6. Cox-model adjusted overall survival without transplant by fibrosis severity. [a]

[a] Survival curves represent adjusted predictions calculated by the Cox proportional regression model adjusted by center and calendar year of patient recruitment.

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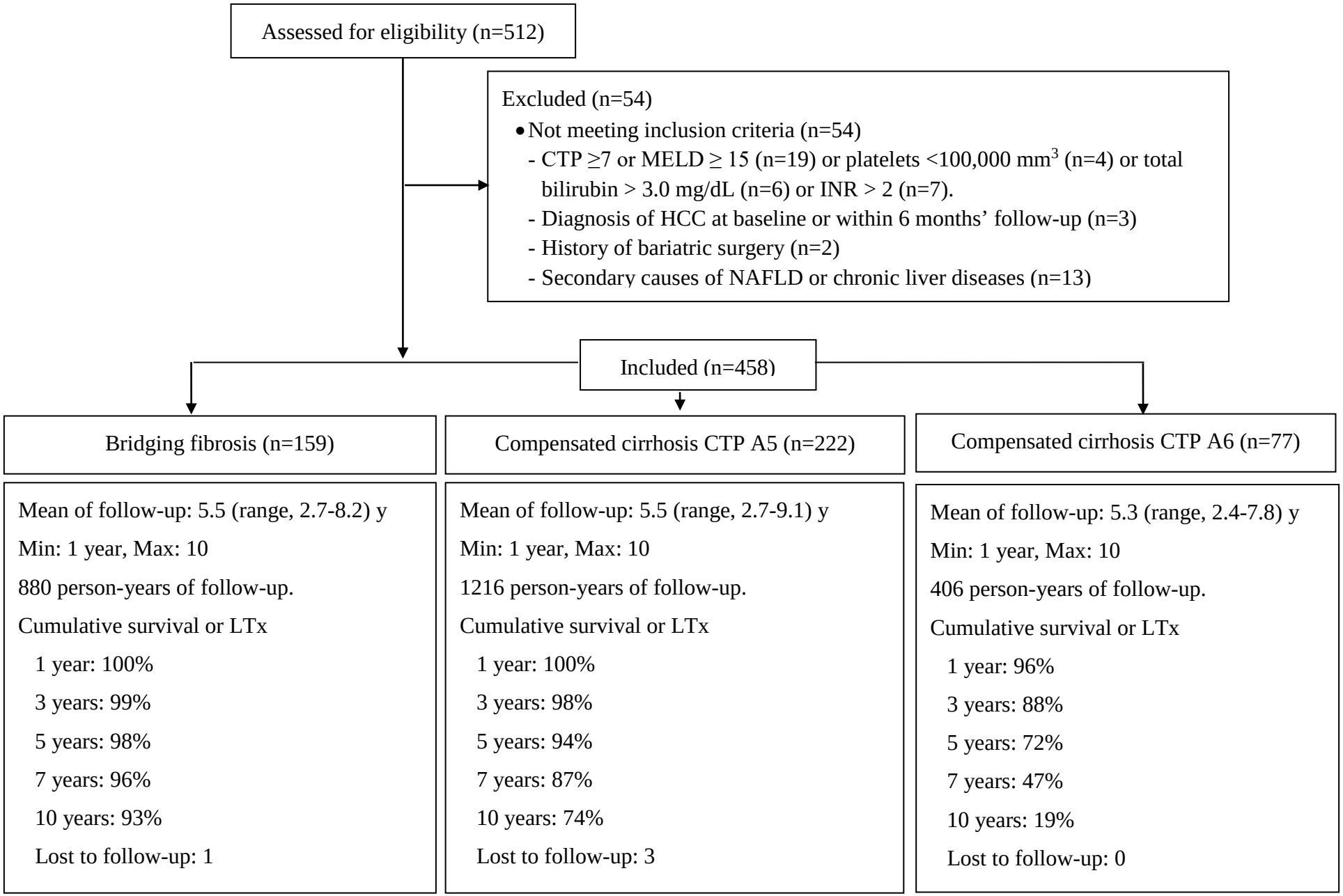
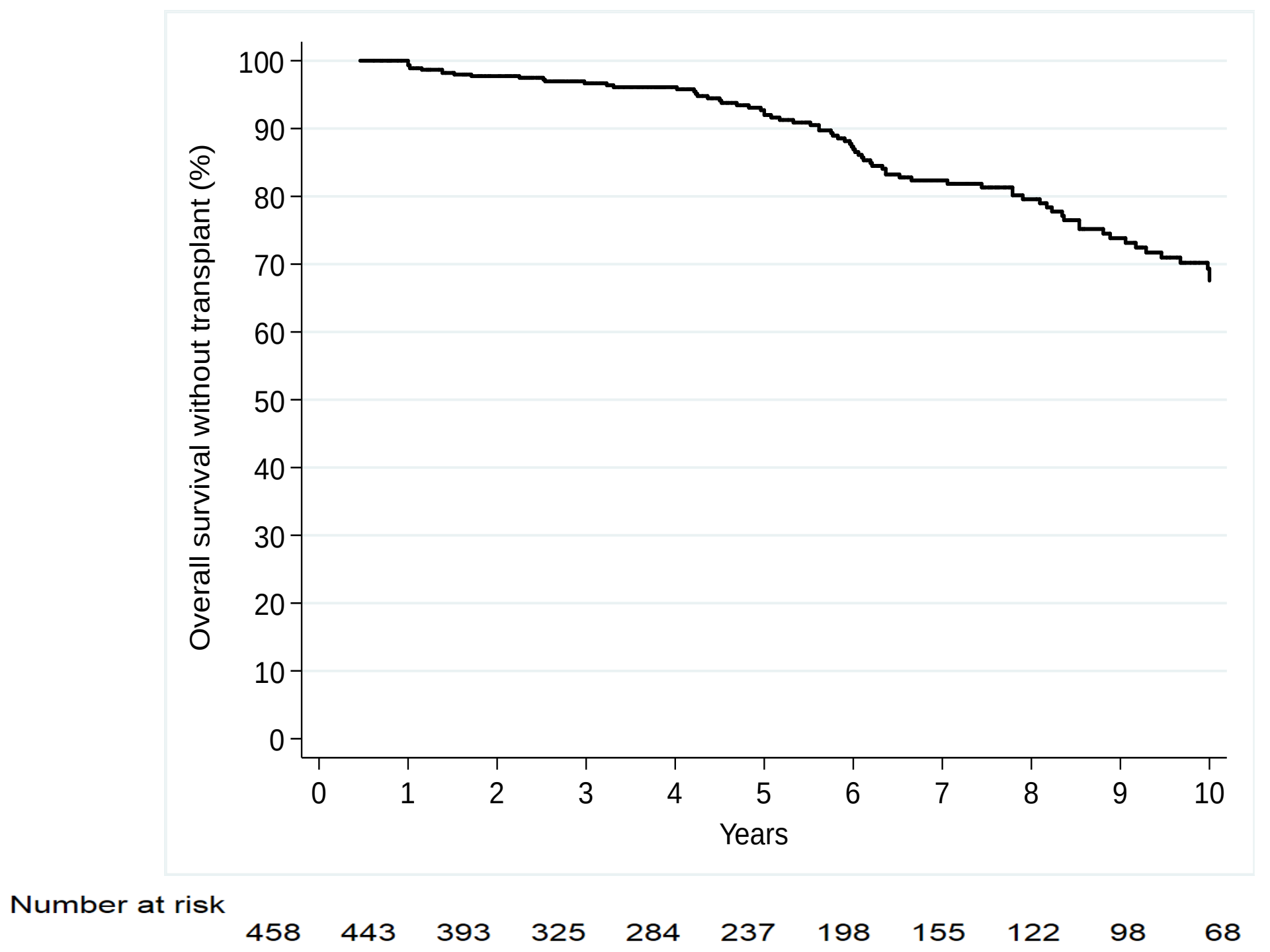
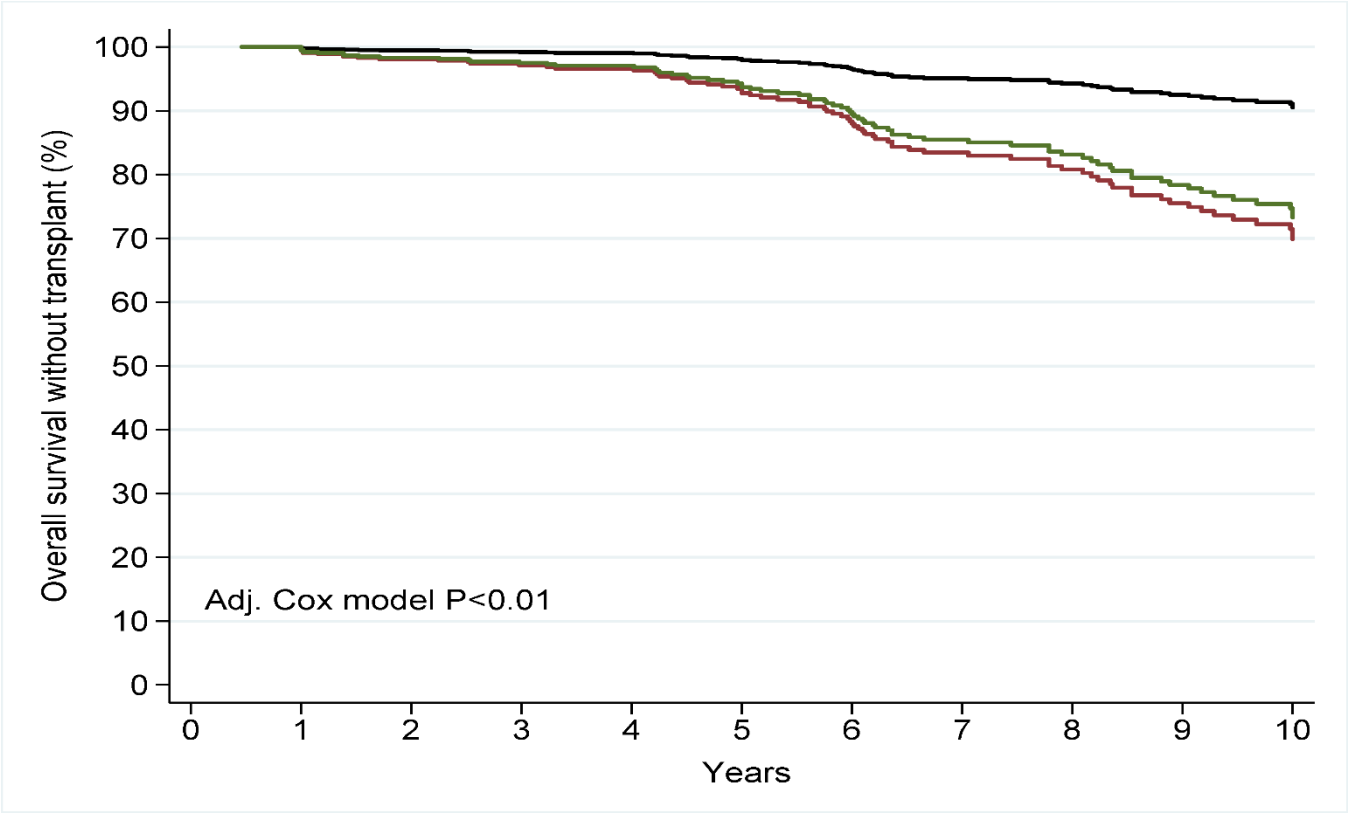
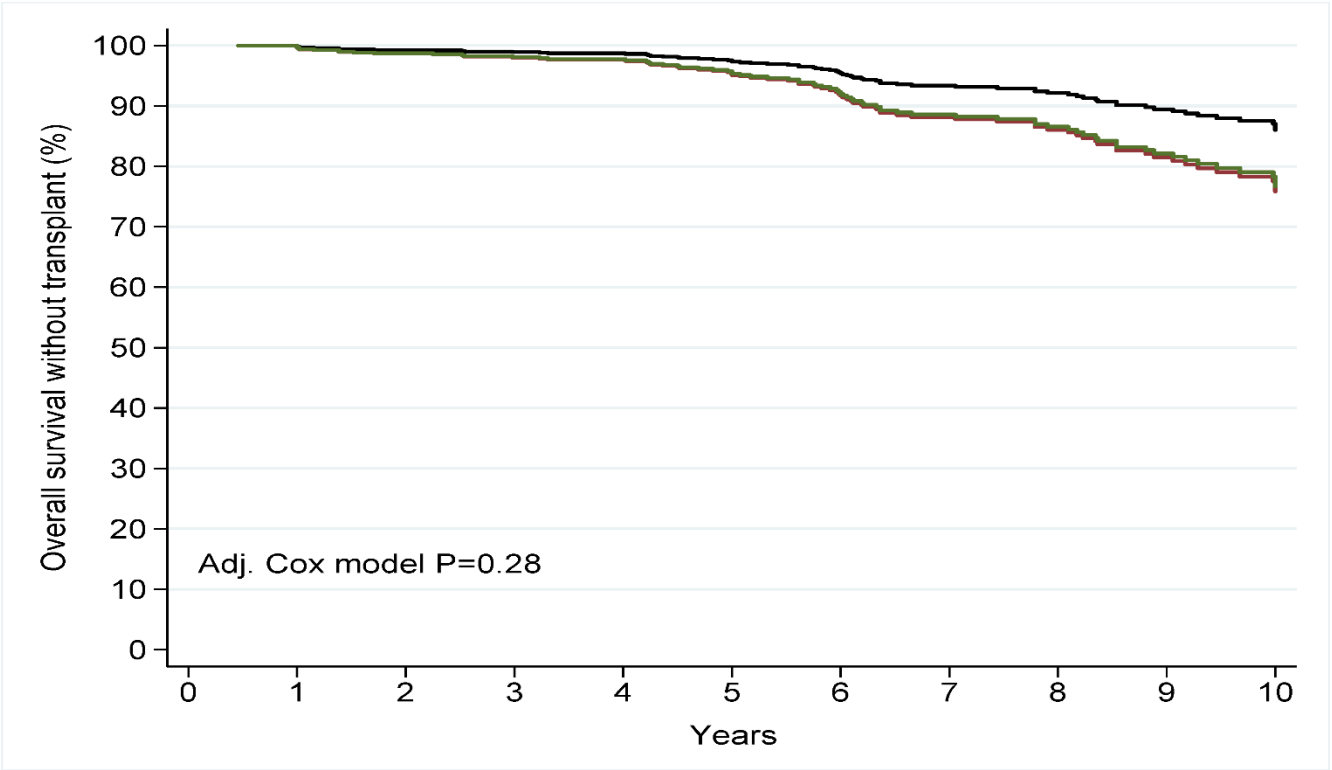

Assessed for eligibility (n=512)
Excluded (n=54)
• Not meeting inclusion criteria (n=54)
- CTP ≥7 or MELD ≥ 15 (n=19) or platelets <100,000 mm3 (n=4) or total bilirubin > 3.0 mg/dL (n=6) or INR > 2 (n=7).
- Diagnosis of HCC at baseline or within 6 months' follow-up (n=3)
- History of bariatric surgery (n=2)
- Secondary causes of NAFLD or chronic liver diseases (n=13)
Included (n=458)
Bridging fibrosis (n=159)
Compensated cirrhosis CTP A5 (n=222)
Compensated cirrhosis CTP A6 (n=77)
Mean of follow-up: 5.5 (range, 2.7-8.2) y
Min: 1 year, Max: 10
880 person-years of follow-up.
Cumulative survival or LTx
1 year: 100%
3 years: 99%
5 years: 98%
7 years: 96%
10 years: 93%
Lost to follow-up: 1
Mean of follow-up: 5.5 (range, 2.7-9.1) y
Min: 1 year, Max: 10
1216 person-years of follow-up.
Cumulative survival or LTx
1 year: 100%
3 years: 98%
5 years: 94%
7 years: 87%
10 years: 74%
Lost to follow-up: 3
Mean of follow-up: 5.3 (range, 2.4-7.8) y
Min: 1 year, Max: 10
406 person-years of follow-up.
Cumulative survival or LTx
1 year: 96%
3 years: 88%
5 years: 72%
7 years: 47%
10 years: 19%
Lost to follow-up: 0


Overall survival without transplant (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
Years
Number at risk
458
443
393
325
284
237
198
155
122
98
68



No. at risk											
Asian	86	86	82	48	39	33	31	27	21	15	4
Non-hispanic White	112	109	82	63	52	39	26	20	15	13	9
Hispanic White	256	244	225	210	189	161	137	104	84	69	54



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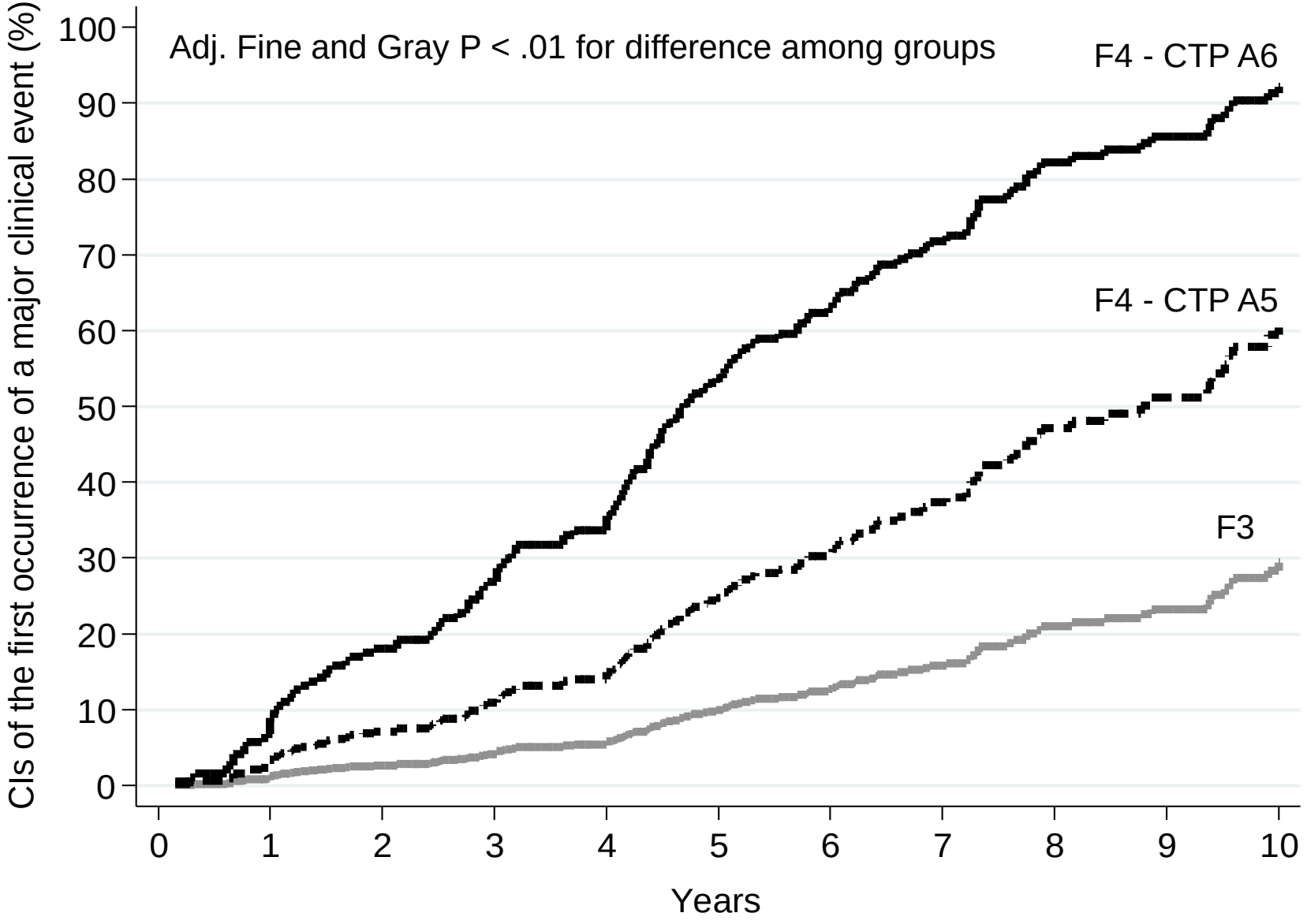
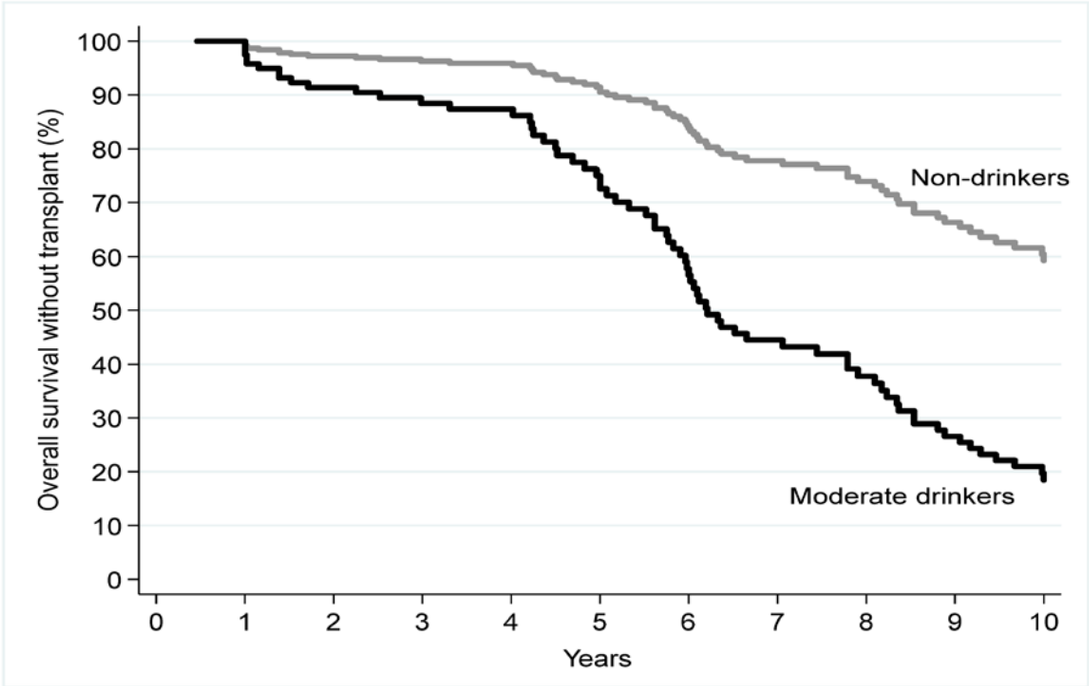
Asian Non-hispanic white Hispanic white

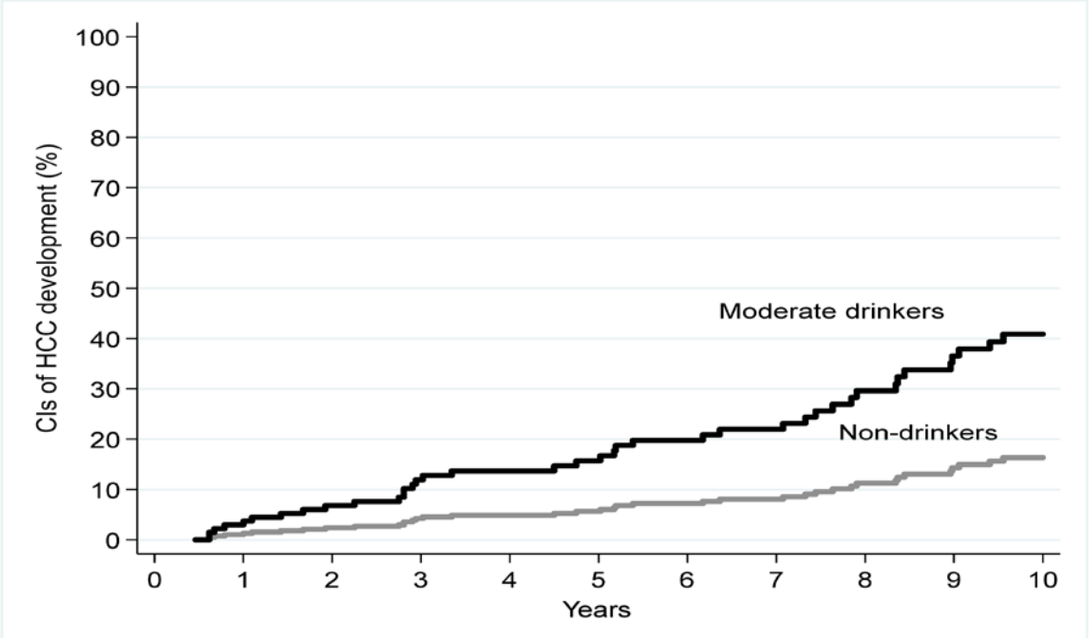


No. at risk

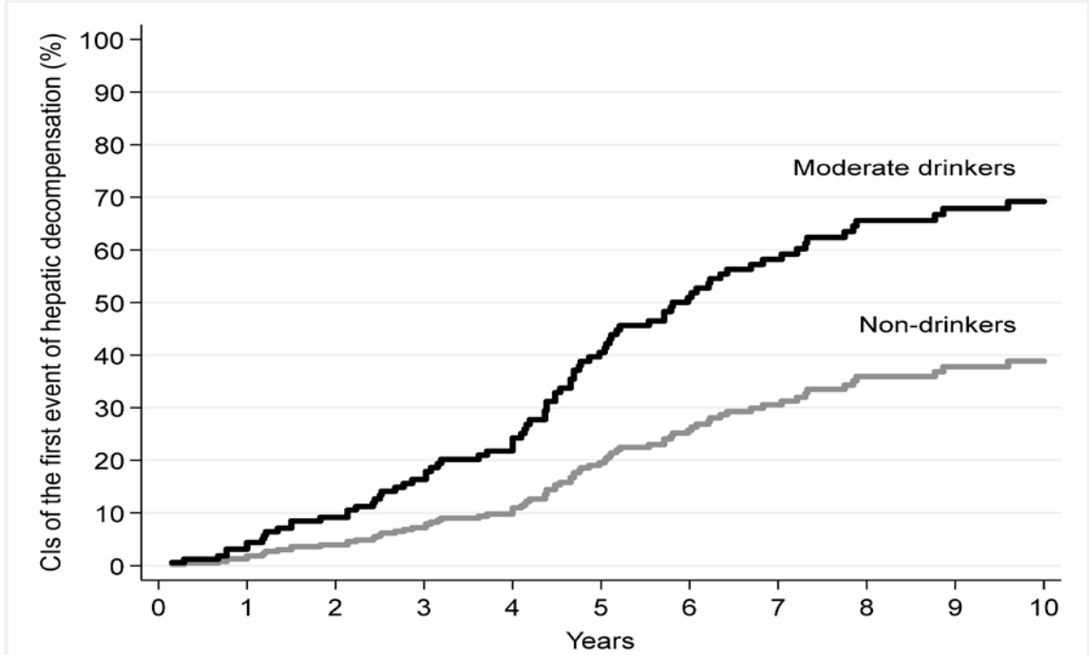
F3	159	153	137	106	92	71	62	44	33	25	11
F4-CTP A5	222	209	183	149	122	93	76	57	36	28	17
F4-CTP A6	77	70	54	43	35	23	12	7	3	3	1



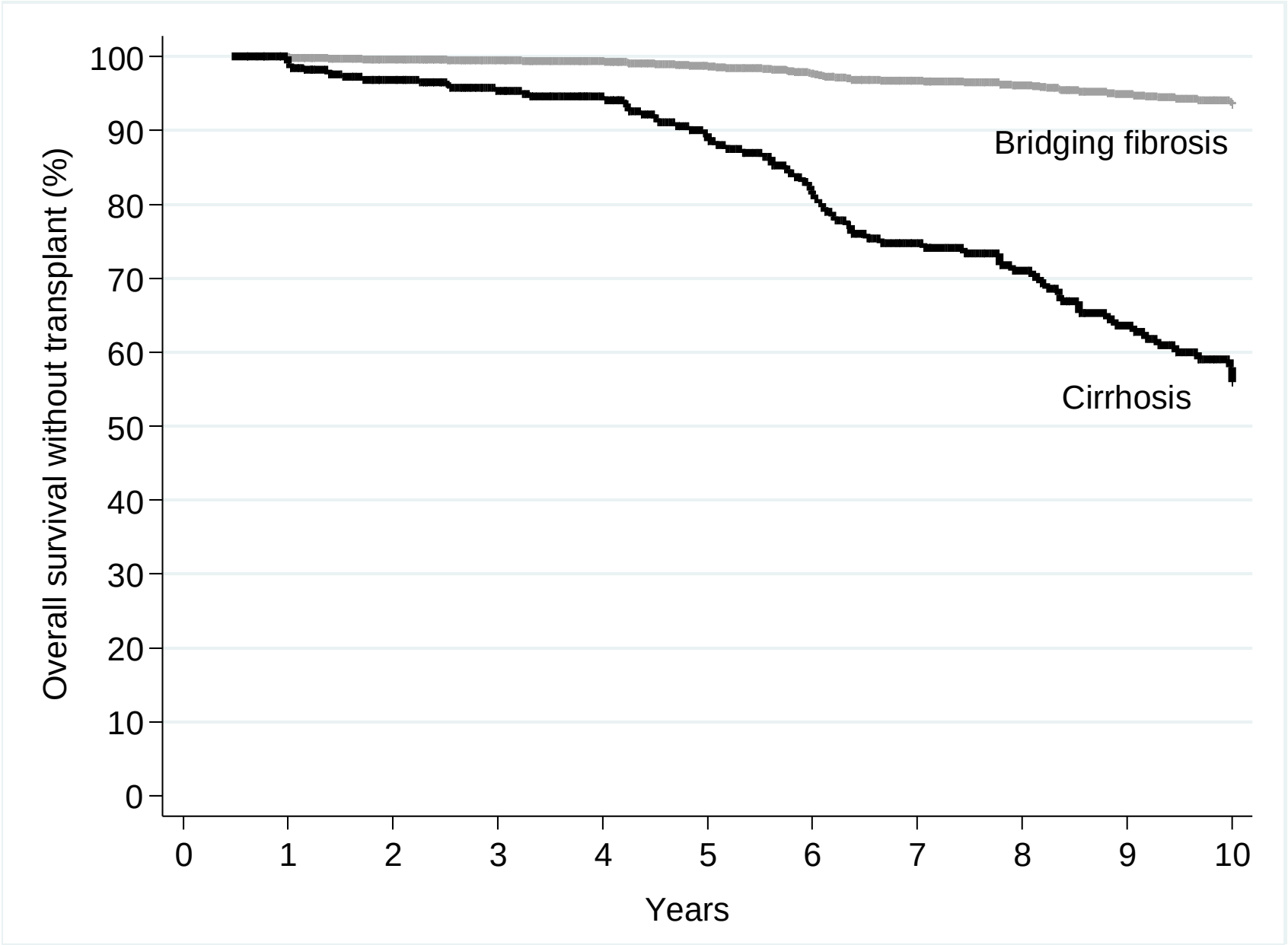
No. at risk											
Non-drinker	259	247	217	184	159	136	110	89	71	58	43
Moderate drinker	40	39	32	26	23	20	16	12	10	9	5



No. at risk											
Non-drinker	259	246	215	180	154	129	103	83	65	51	39
Moderate drinker	40	38	31	24	21	18	13	10	6	5	1



No. at risk											
Non-drinker	259	245	210	174	143	107	82	64	47	42	30
Moderate drinker	40	36	30	22	18	14	11	8	6	5	2



No. at risk											
Bridging fibrosis	159	157	144	115	102	81	72	54	41	31	20
Cirrhosis	299	286	249	210	182	156	126	101	81	67	48

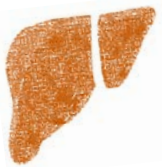
Fibrosis Severity as a Determinant of Cause-specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease

International cohort study

458 biopsy proven NAFLD

Bridging fibrosis
F3 (n=159)

Liver cirrhosis
F4 (n=299)



Annual incidence

Vascular events	0.9
Non-hepatic cancers	1.2

	CTP ***A5***	***A6***
All deaths or OLT	2.1	11.1
Decompensation	3.3	15.6
HCC	1.8	4.7

Risk factors

Liver fat <33%

Moderate alcohol consumption

Cirrhosis

Transplant-free survival

Decompensation

HCC

Gastroenterology