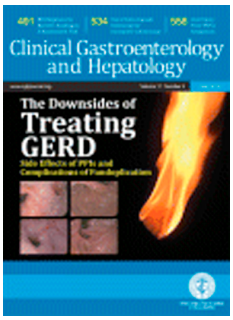


# Effects of Metformin Exposure on Survival in a Large National Cohort of Patients with Diabetes and Cirrhosis

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**Abbreviations:**

ALD – alcoholic liver disease

HBV – hepatitis B virus-related disease

HCC – hepatocellular carcinoma

HCV – hepatitis C virus-related disease

MSM – marginal structural model

NAFLD – nonalcoholic fatty liver disease

NASH – nonalcoholic steatohepatitis

LDL – low density lipoprotein cholesterol

HDL – high density lipoprotein cholesterol

TGL – triglycerides

ABSTRACT: 251 words

**ABSTRACT**

**Background & Aims:** Type II diabetes mellitus worsens the prognosis of cirrhosis. Multiple medications including metformin and statins are often co-administered to manage patients with diabetes. The aim of this study was to assess the impact of metformin exposure on mortality, hepatic decompensation, and hepatocellular carcinoma in individuals with diabetes and cirrhosis, controlling for multiple concomitant exposures.

**Methods:** We performed a retrospective cohort study of patients with cirrhosis diagnosed between January 1, 2008, through June 30, 2016, in the Veterans Health administration. Marginal structural models and propensity matching approaches were implemented to quantify the treatment effect of metformin in patients with pre-existing diabetes with or without prior metformin exposure.

**Results:** Among 74,984 patients with cirrhosis, diabetes mellitus was present prior to the diagnosis of cirrhosis in 53.8% and was diagnosed during follow-up in 4.8%. Prior to the diagnosis of cirrhosis, 11,114 patients had active utilization of metformin. In these patients, metformin, statin, and ACEI/A2RB exposure were independently associated with reduced mortality (metformin HR 0.68 95%CI 0.61-0.75); metformin was not associated with reduced hepatocellular carcinoma (HCC) or hepatic decompensation after adjustment for concomitant statin exposure. For patients with diabetes prior to diagnosis of cirrhosis but no prior metformin exposure, metformin was similarly associated with reduced mortality (HR 0.72 95%CI 0.35-0.97) but not with reduced HCC or hepatic decompensation.

**Conclusions:** Metformin use in patients with cirrhosis and diabetes appears safe and is independently associated with reduced overall but not liver-related mortality, hepatocellular carcinoma or decompensation after adjusting for concomitant statin and ACEI/A2RB exposure.

**KEY WORDS:** human, cirrhosis, diabetes, metformin, statin, alcohol, hepatitis, nonalcoholic steatohepatitis, fatty liver, NAFLD

## INTRODUCTION

Progressive liver injury predisposes to the development of diabetes mellitus (DM), and DM accelerates liver disease progression.[1-4] While 20-40% of patients diagnosed with cirrhosis already carry a diagnosis of DM,[5, 6] of those not yet diagnosed 60% may exhibit insulin resistance or DM on formal testing.[7] DM is a strong risk factor for hepatocellular carcinoma (HCC) in patients with and without known liver disease,[1] and for liver-related death among patients with cirrhosis.[4, 8]

In retrospective studies, the standard first-line treatment for DM, metformin, has been observed to reduce the risk of HCC,[9-13] either via direct anti-neoplastic effects or by suppressing hyperinsulinemia. However the strength of the data remains low. A recent meta-analysis showed reduced all-cause mortality with metformin use in patients with cirrhosis.[14] However, only 3 studies met inclusion criteria, only one of which was prospective with a total N=432.

Diabetic patients are often co-prescribed multiple other medications, such as aspirin, statins, angiotensinogen-converting enzyme inhibitors (ACEI) or angiotensin-2-receptor blockers (A2RB) that might confound the associations of medication exposure and various outcomes, a bias for which adjustment has not been adequately addressed in prior studies.

To address these limitations, we aimed to investigate the impact of metformin exposure on mortality, hepatic decompensation, and HCC in individuals diagnosed with cirrhosis with a pre-existing diagnosis of DM with and without prior metformin utilization. In observational studies, exposures to medications of interest vary over time. Time-varying covariates, such as concomitant medication exposures, and variables that confound an exposure but also may fall in the causal pathway (such as HBA1c and body mass index) cannot be accounted in fixed

regression models without creating immortal time bias and other biases. Using marginal structural modeling (MSM), an approach to estimate the causal effect of an exposure with time-updating confounding,[15] we observed that metformin was independently associated with reduced mortality, but that associations with reduced hepatocellular carcinoma or decompensation were no longer statistically significant after adjustment for concomitant statin exposure.

## METHODS

*Data Sources, Regulatory, Subject Identification*

Clinical data were obtained from VA Corporate Data Warehouse (CDW). Approval was obtained from the Institutional Review Boards at all participating VA sites. Patients with cirrhosis were identified using a validated methodology as previously described based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM) or 10th Revision (ICD10) diagnosis codes.[16, 17] from 1/1/2008 to 12/31/2016 with follow-up through 6/30/2019. Cohort entry date was defined as the first date of the cirrhosis diagnosis entered into the electronic medical record (EMR). Patients were excluded for: fewer than 180 days of clinical follow-up, development of HCC in fewer than 180 days from the diagnosis of cirrhosis, fewer than 2 VA outpatient visits in the index year of diagnosis, age less than 18 or greater than 85 years, or a FIB-4 score < 1.45 (indicating lack of significant fibrosis).[18] The diagnosis of diabetes was based upon the validated algorithm of Butt et al,[19] utilizing ICD9/10 codes, fasting glucose, and diabetes-related medication exposures.

*Covariates*

Baseline laboratory values (see Supplemental Methods) were taken closest to the index date of cirrhosis obtained between 180 days prior to, or 30 days following the diagnosis code. Throughout follow-up , average laboratory values in each quarter of follow-up were used to generate time updating measures of liver disease severity such as the Model for End-Stage Liver Disease-Sodium (MELDNa).[20] Electronic Child-Turcotte-Pugh CTP (eCTP) scores were determined using a validated algorithm.[21] Tobacco use was characterized as current, former, or lifetime non-use using a validated approach.[22] Alcohol use was characterized both by ICD codes as well as Alcohol Use Disorders Identification Test (AUDIT-C);[23] AUDIT-C scores >4 for men and >3 for women were classified as alcohol misuse.[24] Liver disease etiology was assigned per the schema of Beste et al.[25] The Cirrhosis Comorbidity Index was calculated per Jepsen et

al.[26] The presence of hepatic and cardiovascular comorbidities was identified using 1 inpatient or 2 outpatient ICD codes or Common Procedural Terminology (CPT) codes (**Supplemental Table 1**) consistent with published, validated algorithms.[27]

*Outcomes*

Death was ascertained using the Vital Status Master File (censoring as of 6/30/2019).[28] Cause of death (through 12/31/2017) was obtained from the VA Mortality Data Repository,[29] and classified as likely liver-related, diabetes-related, cardiovascular or other (**Supplemental Table 2**). Secondary outcomes included hepatic decompensation using a previously validated algorithm;[30] and HCC using ICD9/10 codes known to be 80% specific for HCC (**Supplemental Table 1**).[31]

*Exposures*

Prescriptions for metformin, statins, ACEI/A2RB, sulfonylureas, nonselective beta blockers, and other relevant medications (see Supplemental Methods) were quantified prior to and following the diagnosis of cirrhosis based on dose and days of medication supplied as previously described.[16] Exposure to medications in each 30-day time-window of follow-up was calculated using the tmerge function of the R survival package using a 30-day delay to avoid protopathic bias (reverse causality).[32] Exposure was considered present if a patient received ≥7 days of medication in a 30-day period.

*Statistical Analysis*

Time-to-event data were compared using the log-rank test and Kaplan-Meier methodology. Marginal structural models (MSM) were fit using inverse probability-of-treatment weighting (IPTW)[15, 33] to correct for time-varying confounding related to the clinical decision to initiate/maintain metformin therapy. Covariates included in the IPTW model were age, gender,

HBA1c (modeled as natural spline with 5 degrees of freedom, **Supplementary Figure 1**), serum albumin, BMI, 10-year cardiovascular risk,[34] prior exposure to metformin, insulin, sulfonylureas, thiazolidinediones, GLP1RAs, and the duration of diabetes. The AUROC for this model was 0.94. Covariate weights were truncated at the 0.01 and 0.99 quantiles (**Supplementary Table 3**). IPTW covariate balance was evaluated in the pseudo-populations generated (**Supplementary Table 4**); covariates for which SMD ≤ 0.1 could not be balanced were included as covariates in outcome models. IPTW weight balance over time are shown in **Supplementary Figure 2**. The associations of metformin exposure and overall mortality, cause-specific mortality, hepatic decompensation (death as competing-risk) and HCC (also competing risk) were estimated in MSM using time-updating Cox proportional hazards models using Fine-Gray estimators for competing risks where relevant. These models were further adjusted for or stratified by Child-Turcotte-Pugh Class and disease etiology, and adjusted for age, gender, race/ethnicity, MELDNa score, tobacco use, AUDIT-C, prior CAD, aspirin, statin, ACEI/A2RB and NSBB exposure (if present), serum cholesterol, and HBA1c. Variables were chosen based on established clinical associations with either liver disease severity or risk of mortality. Covariates for time-varying models were chosen if p was <0.15 in univariable analyses. A two-sided p-value of <0.05 was defined to be statistically significant. To compare effects of different metformin exposures and doses on outcomes, we performed landmark analyses examining the exposure to metformin in terms of days and dose (mg/d) in the first 180 or 360d after cirrhosis diagnosis among patients surviving ≥180 or 360d respectively and assessed subsequent survival and time to HCC in Cox models adjusted for age, etiology, Child-Turcotte-Pugh stage, statin and ACEI/A2RB exposure. Analyses were performed using the Survival and ipw package in R.[32, 33]

*Sensitivity Analyses*

We tested the effect of varying the exposure time within a time window (7/30, 14/30, 21/30 days) for defining exposure on the association of metformin with overall survival. We also assessed the impact of varying HCC latency exclusions (180, 360, 540, and 720 days) on the association of metformin and statins with hepatocellular carcinoma incidence.

## RESULTS

*Patient Groups and Characteristics*

Of an initial cohort of 129,051 patients with new diagnoses of cirrhosis, after exclusion of subjects with fewer than 2 outpatient encounters in the index year, fewer than 180 days of clinical follow-up, and/or FIB-4 < 1.45, a total of 74,984 were analyzed (**Figure 1)**. Of these, 43,674 (58.2%) were diagnosed with diabetes, 40,368 (53.8%) prior to the diagnosis of cirrhosis and 3,660 (4.8%) following the diagnosis of cirrhosis. Of the patients with diabetes prior to cirrhosis, 18,600 received at least 1 prescription of metformin and 21,768 were metformin naïve. A total of 11,527 patients received a prescription for metformin within 90-days of the diagnosis of cirrhosis; 66.8% of active metformin users received new prescriptions within 90 days of diagnosis of cirrhosis and 85.4% were ever re-prescribed metformin during follow-up for a median exposure of 673 days (IQR 250-1320 days). Patients who never resumed metformin exhibited markedly higher rates of morbidity and mortality (HCC rates 5.9 vs. 2.3 per 100 patient-years; decompensation 17.1 vs 9.1; death rate 18.1 vs. 8.8; all $p < 0.0001$, unadjusted data presented in **Supplemental Table 5**).

Among patients with cirrhosis with pre-existing diabetes, metformin-experienced patients were more likely White, obese with NAFLD/NASH, and to have prior cardiovascular disease (coronary artery disease, MACE), to be on concomitant aspirin (41.0 vs 31.5%), statins (62.7% vs. 35.8%), insulin (45.4% vs 26.2%), sulfonylureas, thiazolidinediones, and ACE inhibitors and/or A2RB. They were less likely to have been diagnosed with a prior hepatic decompensation (17.7 vs 22.0%) or treated with a NSBB (**Table 1 and Supplemental Table 6)**.

*Effect of Continuing Metformin in Metformin-experienced Diabetic Patients Diagnosed with Cirrhosis*

We first analyzed the effect of ongoing exposure to metformin among 11,571 metformin-experienced patients with active utilization of metformin within 90 days of cirrhosis diagnosis. A relatively stable fraction (>50%) of prior users continued use during 5 years of follow-up (**Figure 2A**). In 2-way ANOVA, there was no observable effect of metformin on BMI (data not shown). As shown in **Table 2**, after adjustment for covariates, as well as relevant prior and concurrent medication exposures (particularly statins), metformin remained significantly associated with reduced mortality with a HR 0.68 (95%CI 0.61-0.75). Statins, ACEI/A2RB and sulfonylurea therapy, but not aspirin use, were also independently associated with reduced mortality in this cohort (statin HR 0.78 95%CI 0.69-0.87). Varying the definition of exposure from 7 to 14 to 21 days per 30-day window had minimal impact on the estimation of effect size (**Supplemental Table 7**). In models to assess for synergy, we found no evidence of anything other than an additive effect of metformin with statins or metformin with ACEI/A2RB on the outcome of overall mortality (for statin S statistic 0.97 95%CI 0.71-1.31 where S = 1 is pure additive effect; the S statistic for ACEI/A2RB was 0.74 95%CI 0.63-0.87, again < 1 showing no synergy). In stratified analysis, the benefit of metformin on mortality was present in patients with CTP A and B cirrhosis due to HCV, alcohol, and/or NAFLD/NASH but not in the subgroup of patients with cirrhosis due to other causes (**Table 2**). The effect of metformin on overall survival appeared dose-related; in Landmark analysis evaluating metformin exposure in either the first 180 or 360 day of cirrhosis, both cumulative days of exposure (**Figure 2B-C**) and dose received (**Figure 2D-E**) was strongly associated with reduced subsequent risk of death.

*Liver Cancer, Hepatic Decompensation and Cause-specific Mortality*

We next evaluated the effect of metformin, adjusted for concomitant exposures and covariates, on liver-related complications and cause-specific causes of death (**Table 3**). Metformin was not significantly associated with reduced rates of HCC and hepatic decompensation after adjustment for statin exposure and other relevant covariates (**Table 3, Supplemental Table 8-**

**89, Supplemental Figure 3**). The lack of association of metformin with HCC development was insensitive to changes in HCC latency (**Supplemental Table 10**). In MSM but not Landmark competing-risk models, metformin was associated with a reduction in liver-related death (**Table 4**). In both models, metformin was significantly associated with reduced death from diabetes or cardiovascular causes (HR 0.67 95%CI 0.47-0.95, every 30 days of metformin exposure during year 1 associated with HR 0.95 95%CI 0.93-0.98 for diabetes/cardiovascular death, **Table 4, Supplemental Figure 4**).

*Effect of Starting Metformin in Diabetic Patients after Diagnosis with Cirrhosis.*

In patients with cirrhosis and diabetes who had not previously been treated with metformin, metformin was initiated in 3,980 individuals (18%) during follow-up (**Figure 2D**). In adjusted MSM models, metformin remained significantly associated with reduced mortality with HR 0.72 (95%CI 0.63-0.82) but similar to previously exposed cirrhotic patients, metformin was not independently associated with reduced HCC or decompensation (**Supplemental Table 11**).

## DISCUSSION

The analysis of pharmacological exposure outcomes related to diabetes and cirrhosis is challenging due to the timing of diagnosis of diabetes, the possible impact of the diagnosis of cirrhosis itself or manifestations of cirrhosis on prescribing behavior, and multiple potential concomitant therapies for diabetes or related conditions that could also impact cirrhosis-related outcomes.[16, 35, 36] For example, metformin may affect HBA1c, which may be both a predictor of survival as well as indication to start/continue metformin. A patient previously on metformin is also more likely to remain on metformin, and may be more likely to receive other diabetes-related medications and care. MSM, an approach to estimate the causal effect of an exposure using inverse probability of treatment weighting to adjust for time-dependent covariates that are risk factors for, or predictors of, the outcome and also predictors of the exposure of interest were applied in this study to adjust as much as possible for time-dependent confounding by indication.[15, 37]

In this large cohort of patients with cirrhosis, DM was present at baseline in 53.8% and was diagnosed during follow-up in an additional 4.8%. Fewer than half of patients with known diabetes had any exposure to metformin prior to being diagnosed with cirrhosis. Of those actively using metformin, the diagnosis of cirrhosis was temporally associated with permanent discontinuation of metformin in 14.5%. From administrative data, it is not possible to ascertain the reason for medication discontinuation. Exposure to metformin after cirrhosis diagnosis was associated with reduced mortality even after adjusting for other commonly utilized medications in the diabetic and/or cirrhosis population such as aspirin, statins, ACEI/A2RB, and NSBB. Child-Turcotte-Pugh A and B (but not C) patients appeared to benefit. The magnitude of the hazard ratio of metformin for mortality ranged from 0.65-0.72 for the specific subpopulations evaluated and was dose dependent. This hazard ratio is a more conservative estimate than that found in a non-randomized prospective cohort of 250 diabetic patients with cirrhosis in which

metformin was either continued or not (HR 0.43 95%CI 0.24-0.78)[38], likely due to the nonrandomized nature and effect of confounders incompletely controlled in the prior study. We could not observe an impact of metformin on liver-related outcomes such as HCC, hepatic decompensation, or liver-related death but found a strong association with reduced cardiovascular mortality (HR 0.58 95%CI 0.39-0.87), as has been observed in some but not all meta-analyses of metformin use in non-cirrhosis settings.[39, 40]

In prior observational studies, metformin use has most strongly been associated with reduced rates of liver cancer in patients with cirrhosis,[9-12] chronic hepatitis B,[41] or diabetes[42, 43] with hazard ratios ranging from 0.19-0.49. Metformin directly inhibits the growth of HCC cell lines *in vitro* and in animal models,[44] and may also reduce hepatic fibrogenesis.[45] In a large population-based study from Taiwan, Chen et al.[12] reported a 21% decrease in the risk of HCC in diabetic patients exposed to metformin after multiple adjustments, but not controlling for concomitant statin use. In another study using the Taiwanese national database, after adjustment for statin exposure, an apparent protective effect of metformin in univariable analysis disappeared while statins remained significantly associated with reduced HCC risk.[35, 46] Similarly, we found no demonstrable impact of metformin on HCC or hepatic decompensation events after adjusting for concomitant statin utilization, further supporting the argument that statin co-utilization has confounded the prior evidence for metformin as a chemopreventive agent for HCC in population-level studies.

Discontinuation of medications in patients with liver disease is a common practice due to the perceived threat of altered hepatic metabolism and toxicity. Indeed, the Food and Drug

As with any observational cohort study, unmeasured confounding and residual confounding by indication cannot be excluded. There is no active comparator for metformin use and we did not

formally compare metformin plus statin to metformin without statins. This was a study of mostly male U.S. Veterans who are older, may be more affected by medical comorbidities, and have worse outcomes than the general U.S. population. While we did adjust for aspirin, statins, other diabetes therapies, ACEI/A2RB and NSBB use, there are other medication exposures that could confound the association of metformin with survival outcomes. Finally, we had a small representation of Child-Turcotte-Pugh C patients limiting the strength of inferences related to treatment effect in this subgroup.

**CONCLUSIONS:**

In this large cohort of patients with cirrhosis, diabetic patients exposed to metformin exhibited dose-dependent reduced mortality (HR 0.57-0.87) even after adjusting for the concomitant use of aspirin, statins, ACEI/A2RB, and NSBBs. Contrasting with some prior studies, no significant effect of metformin was observed on the reduction of HCC, hepatic decompensation, or liver-related death after adjusting for concomitant statin and ACEI/A2RB exposure. Metformin use was generally safe. Similar to the general diabetic population, metformin should be utilized when appropriate in diabetic patients with cirrhosis for improvement of overall, but not necessarily liver-related, survival. .

**FIGURE LEGENDS**

**Figure 1.** Cohort identification and grouping for analysis.

**Figure 2. Effect of Metformin Continuation in Existing Users. A.** Persistence of metformin utilization among metformin-experienced patients with cirrhosis over the course of follow-up. Red line indicates percentage surviving. **B**. Effect of continued metformin exposure in days on relative risk of death in Landmark analysis evaluating first 360 days in metformin-experienced patients. Weighted (gray) and unweighted analysis (black) are shown. **C**. Effect of continued metformin exposure in cumulative dose (mg) on relative risk of death in Landmark analysis evaluating first 360 days in metformin-experienced patients. **D-F.** Parallel analysis to A-C for metformin-naïve diabetic patients with cirrhosis.

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## TABLES.

Table 1. Baseline Characteristics of Patients with Cirrhosis and Pre-Existing Diabetes

| | Diabetes Preceding Cirrhosis Prior Metformin | | |
|---|---|---|---|
| | No | Yes | p |
| N | 23228 | 19301 | |
| Age, Median (IQR) | 62 (57-67) | 63 (58-67) | <0.0001 |
| Gender, Male, N (%) | 22695 (97.7%) | 18715 (97.0%) | <0.0001 |
| Race/Ethnicity, N (%) | | | <0.0001 |
| White | 12863 (55.4%) | 11610 (60.2%) | |
| Black | 4830 (20.8%) | 3249 (16.8%) | |
| Hispanic | 1928 (8.3%) | 1567 (8.1%) | |
| Other/Unknown | 3607 (15.5%) | 2875 (14.9%) | |
| Etiology, N (%) | | | <0.0001 |
| HCV + Alcohol | 6081 (26.2%) | 4195 (21.7%) | |
| HCV | 3444 (14.8%) | 2445 (12.7%) | |
| Alcohol | 7650 (32.9%) | 6448 (33.4%) | |
| NAFLD/NASH | 4614 (19.9%) | 5123 (26.5%) | |
| Other | 1439 (6.2%) | 1090 (5.6%) | |
| AUDIT-C > 4 in prior year, N (%) | 3327 (14.3%) | 2336 (12.1%) | 0.013 |
| HIV+, N (%) | 460 (2.0%) | 258 (1.3%) | <0.0001 |
| Managed at Academic Center, N (%) | 13427 (57.8%) | 10822 (56.1%) | 0.005 |
| Seen by Hepatologist, N (%) | 3994 (17.2%) | 3480 (18.0%) | <0.0001 |
| Body Mass Index, Median (IQR) | 28.2 (24.5-32.5) | 30.3 (26.4-34.6) | 0.22 |
| Body Mass Class, N (%) | | | <0.0001 |
| Underweight | 760 (3.3%) | 308 (1.6%) | |
| Ideal | 5261 (22.6%) | 2735 (14.2%) | |
| Overweight | 7856 (33.8%) | 5861 (30.4%) | |
| Obese | 9351 (40.3%) | 10397 (53.9%) | |
| Child-Turcotte-Pugh Score, Median (IQR) | 6 (5-7) | 6 (5-7) | <0.0001 |
| MELDNa Score, Median (IQR) | 9 (7-12) | 8 (7-11) | <0.0001 |
| Decompensated at Cirrhosis Diagnosis, N (%) | 4931 (21.2%) | 3393 (17.6%) | <0.0001 |
| Duration of diabetes, Median Days (IQR) | 1958 (659-3132) | 2706 (1556-3706) | <0.0001 |
| Dyslipidemia, N (%) | 21192 (91.2%) | 18780 (97.3%) | <0.0001 |
| Hypertension, N (%) | 22261 (95.8%) | 19135 (99.1%) | <0.0001 |
| Pre-Existing CAD, N (%) | 5916 (25.5%) | 5782 (30.0%) | <0.0001 |
| Cumulative Metformin Exposure prior to cirrhosis, Median (IQR) | 0 (0-0) | 670 (248-1316) | <0.0001 |
| Cumulative Metformin Exposure after cirrhosis, Median (IQR) | 0 (0-0) | 272 (0-876) | <0.0001 |
| Metformin stopped > 90d before Cirrhosis, N (%) | 0 (0.0%) | 7312 (37.9%) | <0.0001 |
| Metformin filled within 90d after Cirrhosis, N (%) | 855 (3.7%) | 8751 (45.3%) | <0.0001 |
| Any Metformin after Cirrhosis, N (%) | 4740 (20.4%) | 12408 (64.3%) | <0.0001 |
| Prior Exposure to Statin, N (%) | 8166 (35.2%) | 12055 (62.5%) | <0.0001 |
| Prior Exposure to Insulin, N (%) | 5910 (25.4%) | 8751 (45.3%) | <0.0001 |
| Prior Exposure to Sulfonylurea, N (%) | 5098 (21.9%) | 11626 (60.2%) | <0.0001 |
| Prior Exposure to TZD, N (%) | 503 (2.2%) | 1818 (9.4%) | <0.0001 |
| Prior Exposure to DPP4, N (%) | 75 (0.3%) | 294 (1.5%) | <0.0001 |
| Prior Exposure to GLP1, N (%) | 21 (0.1%) | 88 (0.5%) | <0.0001 |
| Prior Exposure to Other Anti-Diabetes, N (%) | 171 (0.7%) | 605 (3.1%) | <0.0001 |
| Follow-up Time, Median (IQR) | 1232 (653-2084) | 1142 (631-1892) | <0.0001 |

Table 2. Univariable and Multivariable Cox Proportional Hazards for Death

| Model | At-risk/Events 11,527 / 3,885<br>Variable | Univariate<br>HR (95%CI) | p | Multivariate<br>HR (95%CI) | p |
|---|---|---|---|---|---|
| 1* | **Exposure to Metformin, Time-Updating** | **0.42 (0.38-0.46)** | **<0.0001** | **0.68 (0.61-0.75)** | **<0.0001** |
| | Exposure to Statin, Time-Updating | 0.53 (0.50-0.56) | <0.0001 | 0.71 (0.64-0.80) | <0.0001 |
| | Exposure to ACEI/A2RB, Time-Updating | 0.40 (0.36-0.43) | <0.0001 | 0.60 (0.54-0.66) | <0.0001 |
| 2‡ | **CTP A** | | | **0.54 (0.48-0.60)** | **<0.0001** |
| | **CTP B** | | | **0.68 (0.57-0.81)** | **<0.0001** |
| | **CTP C** | | | **0.55 (0.30-1.02)** | **0.06** |
| 3° | **HCV + ETOH** | | | **0.58 (0.46-0.74)** | **0.0004** |
| | **HCV** | | | **0.58 (0.41-0.80)** | **<0.0001** |
| | **ETOH** | | | **0.75 (0.65-0.88)** | **0.0003** |
| | **NAFLD/NASH** | | | **0.58 (0.48-0.68)** | **<0.0001** |
| | **Other Etiology** | | | **0.66 (0.43-1.01)** | **0.053** |
| 4¶ | **Cumulative Exposure to Metformin, Time-Updating (per year)** | **0.82 (0.80-0.83)** | **<0.0001** | **0.955 (0.924-0.987)** | **0.007** |
| 1* | Age | 1.03 (1.03-1.04) | <0.0001 | 1.03 (1.02-1.04) | <0.0001 |
| | Etiology | | | | |
| | HCV+EtOH | REF | | REF | |
| | HCV | 1.04 (0.93-1.15) | 0.52 | 1.34 (1.13-1.59) | 0.0008 |
| | EtOH | 1.30 (1.20-1.41) | <0.0001 | 1.26 (1.10-1.45) | 0.0008 |
| | NAFLD/NASH | 1.46 (1.34-1.58) | <0.0001 | 1.52 (1.30-1.77) | <0.0001 |
| | Other | 1.21 (1.07-1.38) | 0.004 | 1.20 (0.95-1.52) | 0.10 |
| | HCV DAA after diagnosis, Time-Updating | 0.41 (0.36-0.46) | <0.0001 | 0.73 (0.59-0.90) | 0.003 |
| | Child-Turcotte-Pugh Class (Time-Updating) | | | | |
| | A | REF | | REF | |
| | B | 5.01 (4.71-5.32) | <0.0001 | 2.74 (2.46-3.04) | <0.0001 |
| | C | 16.17 (13.96-18.72) | <0.0001 | 7.03 (5.42-9.12) | <0.0001 |
| | MELDNa, Time-Updating (per unit) | 1.14 (1.13-1.15) | <0.0001 | 1.04 (1.03-1.06) | <0.0001 |
| | Hemoglobin A1c, Time-Updating (per unit) | splined | <0.0001 | splined | <0.01 |
| | Tobacco Use Status | | | | |
| | Never User | REF | | REF | |
| | Former User | 1.16 (1.08-1.26) | 0.0002 | 1.21 (1.07-1.36) | 0.002 |
| | Current User | 1.35 (1.26-1.45) | <0.0001 | 1.59 (1.40-1.81) | <0.0001 |
| | Unknown | 1.54 (1.21-1.95) | 0.0004 | 1.76 (1.31-2.37) | 0.0001 |
| | Hypertension | | | | |
| | No | REF | | REF | |
| | Yes | 1.02 (0.79-1.31) | 0.91 | 1.14 (0.98-1.34) | 0.10 |
| | Coronary Artery Disease | | | | |
| | No | REF | | REF | |
| | Yes | 1.32 (1.24-1.40) | <0.0001 | 1.21 (1.09-1.34) | 0.0003 |
| | AUDIT-C ≥ 4 in year prior to cirrhosis | | | | |
| | No | REF | | REF | |
| | Yes | 1.17 (1.07-1.27) | 0.0003 | 1.18 (1.01-1.37) | 0.02 |
| | Total Cholesterol, mg/dl, Time-Updating (per unit) | 0.99 (0.99-0.99) | <0.0001 | 0.99 (0.99-0.99) | <0.0001 |
| | Cumulative Exposure to Meformin before Cirrhosis (per year) | 1.01 (0.99-1.02) | 0.30 | 1.00 (0.99-1.00) | 0.33 |
| | Exposure to Insulin, Time-Updating | 1.05 (0.99-1.11) | 0.10 | 1.06 (0.95-1.18) | 0.25 |
| | Exposure to Sulfonylurea, Time-Updating | 0.66 (0.61-0.70) | <0.0001 | 0.90 (0.80-1.01) | 0.08 |
| | Exposure to TZD, Time-Updating | 0.53 (0.37-0.74) | <0.0001 | 0.81 (0.55-1.19) | 0.29 |
| | Exposure to GLP1, Time-Updating | 0.42 (0.24-0.76) | 0.004 | 0.69 (0.44-1.08) | 0.10 |
| | Exposure to DPP4, Time-Updating | 0.55 (0.42-0.72) | <0.0001 | 0.74 (0.41-1.35) | 0.33 |

* Model 1 covariates include gender, race/ethnicity, Cirrhosis comorbidity score, body mass index class, academic affiliation of managing center, frequency of low socioeconomic status at the managing center ‡ Model 1 stratifed by time-updated Child-Turcotte-Pugh class ° Model 1 stratified by disease etiology ¶ Model evaluates cumulative exposure to Metformin (in years) as a time-updating covariate with identical covariates to Model 1.

Table 3. Impact of Metformin and other medications on HCC, decompensation and MACE

| HCC[*] | At-risk/ Events | HR | p |
|---|---|---|---|
| Exposure to Metformin, Time-Updating | 11,246 / | 0.98 (0.81-1.18) | 0.86 |
| Exposure to Statin, Time-Updating | 856 | **0.74 (0.60-0.90)** | **0.003** |
| Exposure to Insulin, Time-Updating | | **1.41 (1.15-1.72)** | **0.001** |
| Exposure to Sulfonylurea, Time-Updating | | 1.16 (0.96-1.40) | 0.11 |
| Decompensation[*,§] | At-risk/ Events | HR | p |
| Exposure to Metformin, Time-Updating | 8,088 / | 1.06 (0.82-1.09) | 0.43 |
| Exposure to Statin, Time-Updating | 1,545 | **0.78 (0.68-0.90)** | **0.0007** |
| Exposure to Insulin, Time-Updating | | **1.19 (1.01-1.41)** | **0.034** |
| Exposure to Sulfonylurea, Time-Updating | | 1.07 (0.93-1.23) | 0.37 |
| MACE[*,†] | At-risk/ Events | HR | p |
| Exposure to Metformin, Time-Updating | 9,833 / | 1.00 (0.83-1.23) | 0.93 |
| Exposure to Statin, Time-Updating | 663 | 1.09 (0.89-1.34) | 0.39 |
| Exposure to Insulin, Time-Updating | | 1.18 (0.95-1.45) | 0.12 |
| Exposure to Sulfonylurea, Time-Updating | | 1.15 (0.94-1.41) | 0.17 |

*Models adjutsed for age, gender, race/ethnicity, disease etiology, Child-Turcotte-Pugh stage, MELDNa, platelet count, AST, ALT, academic affiliation of treatment site, socioeconomic indicator, baseline history of CAD § Child-Turcotte-Pugh A patients only † Analysis includes only patients with no previous MACE events.

Table 4. Effect of Metformin on Liver-related and Diabetes/Cardiovascular Death in Landmark Competing Risk and MSM models

| Cohort/Outcome | Outcome | At-Risk/Events | Analysis | | Exposure | HR (95%CI) | p |
|---|---|---|---|---|---|---|---|
| Metformin-experienced | Liver-related death or transplant[1] | 10,238 / 858 | Univariable | Landmark | **Metformin exposure, per 30 days** | **0.98 (0.96-0.99)** | **0.03** |
| | Liver-related death | 11,527 / 637 | | MSM | **Metformin exposure, time-updating** | **0.34 (0.27-0.43)** | **<0.0001** |
| | Liver-related death or transplant[1] | 10,238 / 858 | Multivariable[3] | Landmark | Metformin exposure, per 30 days | 0.99 (0.98-1.01) | 0.89 |
| | | | | | Statin exposure, per 30 days | 0.94 (0.93-0.96) | <0.0001 |
| | | | | | ACEI exposure, per 30 days | 1.00 (0.99-1.02) | 0.18 |
| | Liver-related death | 11,527 / 637 | Multivariable[4] | MSM | **Metformin exposure, time-updating** | **0.65 (0.51-0.84)** | **0.001** |
| | | | | | Statin exposure, time-updating | 0.47 (0.35-0.64) | <0.0001 |
| | | | | | ACEI/A2RB exposure, time-updating | 0.51 (0.40-0.66) | <0.0001 |
| | Diabetes/Cardiovascular death[2] | 10,238 / 341 | Univariable | Landmark | **Metformin exposure, per 30 days** | **0.96 (0.94-0.98)** | **0.002** |
| | Diabetes/Cardiovascular death | 11,527 / 374 | | MSM | **Metformin exposure, time-updating** | **0.53 (0.39-0.72)** | **<0.0001** |
| | Diabetes/Cardiovascular death[2] | 10,238 / 341 | Multivariable[3] | Landmark | **Metformin exposure, per 30 days** | **0.95 (0.93-0.98)** | **0.0009** |
| | | | | | Statin exposure, per 30 days | 1.01 (0.99-1.04) | 0.06 |
| | | | | | ACEI exposure, per 30 days | 1.01 (0.99-1.03) | 0.21 |
| | Diabetes/Cardiovascular death | 11,527 / 374 | Multivariable[4] | MSM | **Metformin exposure, time-updating** | **0.67 (0.47-0.95)** | **0.02** |
| | | | | | Statin exposure, time-updating | 0.88 (0.62-1.25) | 0.49 |
| | | | | | ACEI/A2RB exposure, time-updating | 0.89 (0.64-1.25) | 0.52 |

[1] Diabetes/Cardiovascular death as competing-risk

[2] Liver-related death or transplant as competing-risk

[3] Adjusted for age, race/ethnicity, etiology, Child-Turcotte-Pugh Score

[4] Adjusted for age, race/ethnicity, etiology, Child-Turcotte-Pugh Score, exposure to aspirin, other diabetes therapies, MELDNa, FIB4, Circom, smoking, prior CAD, AUDIT-C, BMI, HCV DAA therapy , HBA1c, Total cholesterol, prior metformin exposure and prior insulin exposure; HR for cardiovascular death alone 0.58 95%CI 0.39-0.87.