Continuation of Metformin Use After a Diagnosis of Cirrhosis Significantly Improves Survival of Patients With Diabetes

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The risks and benefits of metformin use in patients with cirrhosis with diabetes are debated. Although data on a protective effect of metformin against liver cancer development have been reported, metformin is frequently discontinued once cirrhosis is diagnosed because of concerns about an increased risk of adverse effects of metformin in patients with liver impairment. This study investigated whether continuation of metformin after cirrhosis diagnosis improves survival of patients with diabetes. Diabetic patients diagnosed with cirrhosis between 2000 and 2010 who were on metformin at the time of cirrhosis diagnosis were identified (n = 250). Data were retrospectively abstracted from the medical record. Survival of patients who continued versus discontinued metformin after cirrhosis diagnosis was compared using the log-rank test. Hazard ratio (HR) and 95% confidence interval (CI) were calculated using Cox’s proportional hazards analysis. Overall, 172 patients continued metformin whereas 78 discontinued metformin. Patients who continued metformin had a significantly longer median survival than those who discontinued metformin (11.8 vs. 5.6 years overall, \( P < 0.0001 \); 11.8 vs. 6.0 years for Child A patients, \( P = 0.006 \); and 7.7 vs. 3.5 years for Child B/C patients, \( P = 0.04 \), respectively). After adjusting for other variables, continuation of metformin remained an independent predictor of better survival, with an HR of 0.43 (95% CI: 0.24-0.78; \( P = 0.005 \)). No patients developed metformin-associated lactic acidosis during follow-up. Conclusion: Continuation of metformin after cirrhosis diagnosis reduced the risk of death by 57%. Metformin should therefore be continued in diabetic patients with cirrhosis if there is no specific contraindication.

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Cirrhosis is responsible for over 29,000 deaths annually in the United States and 1 million deaths annually worldwide, making it the 12th leading cause of mortality both in the United States and globally.¹,² The prevalence of type 2 diabetes in patients with cirrhosis has been reported as 37%, five times greater than in those without cirrhosis.³ Patients with cirrhosis with diabetes have a greater risk of liver-related complications and death than patients with cirrhosis.
without diabetes.\textsuperscript{4-9} Similarly, the risk of death from cirrhosis among diabetic patients was greater than in the general population, with a standardized mortality ratio of 2.5, which is even higher than the mortality ratio of 1.3 conferred by cardiovascular disease in patients with diabetes.\textsuperscript{10} Therefore, it is important to improve cirrhosis-related mortality in diabetic patients.

Metformin, a commonly prescribed oral hypoglycemic agent, has a protective effect against cancer development and cancer mortality in type 2 diabetic patients.\textsuperscript{11-13} Metformin use was associated with a decreased risk of hepatocellular carcinoma (HCC) development in diabetic patients with chronic liver disease (CLD).\textsuperscript{14} Metformin was also independently associated with a reduction in HCC incidence and liver-related death in patients with type 2 diabetes and hepatitis C virus (HCV)-induced cirrhosis.\textsuperscript{15}

Nonalcoholic fatty liver disease (NAFLD) appears to partially mediate an increased risk of liver-related death among patients with diabetes. The presence of NAFLD increased deaths in diabetic patients, with a hazard ratio (HR) of 2.2, with 19\% of deaths being liver related.\textsuperscript{16} Metformin prevented and reversed steatosis and inflammation in a nondiabetic mouse model of nonalcoholic steatohepatitis (NASH)\textsuperscript{17} and improved liver histology and alanine aminotransferase (ALT) levels in patients with NASH.\textsuperscript{18,19}

Because of theoretical concerns about the increased risk of lactic acidosis in diabetic patients with CLD, many clinicians are reluctant to prescribe metformin for diabetic patients with CLD and some recommend discontinuation of metformin after the diagnosis of cirrhosis. However, the evidence that metformin induces liver injury is weak.\textsuperscript{20} The incidence of lactic acidosis in diabetic patients treated with metformin is low, with approximately 0.03-0.5 cases per 1,000 patient-years, and the incidence of lactic acidosis among diabetic patients who take metformin does not differ from the incidence in diabetic patients not receiving metformin.\textsuperscript{21-23} In addition, the published reports of lactic acidosis in patients with liver disease are largely restricted to case reports of patients with cirrhosis who were actively drinking alcohol.\textsuperscript{24} Thus, these patients may not represent the general population with cirrhosis and diabetes.

Given the potential beneficial effects of metformin on liver inflammation and carcinogenesis, we hypothesized that continuation of metformin use after the diagnosis of cirrhosis would improve the survival outcome of diabetic patients. The primary aim of our study was to assess the survival difference between diabetic patients who continued taking metformin versus those who discontinued metformin after cirrhosis diagnosis. We also investigated other factors determining survival outcomes in patients with cirrhosis with diabetes.

**Patients and Methods**

**Patients.** All diabetic patients diagnosed with cirrhosis between January 1, 2000 and December 31, 2010 and who were on metformin at cirrhosis diagnosis were included in this study (n = 250). Patients were categorized into two groups, that is, (1) those who continued metformin after cirrhosis diagnosis and (2) those who discontinued metformin after cirrhosis diagnosis. Continuation of metformin use was defined as taking metformin for at least 3 months after cirrhosis diagnosis, and discontinuation of metformin use was defined as cessation of metformin within a 3-month period after the diagnosis of cirrhosis. The 3-month period was arbitrarily chosen as a cutoff to allow time for health care providers to decide whether to continue or discontinue metformin. Metformin was typically discontinued within this time frame after cirrhosis diagnosis in our cohort.

The diagnosis of cirrhosis was ascertained by histology (n = 124) and/or by clinical features, namely, portal hypertension (PH), morphologic characteristics consistent with cirrhosis in cross-sectional radiologic images (small-sized nodular liver + caudate lobe hypertrophy as well as PH indicated by the presence of collateral vessels, varices, and/or splenomegaly), and/or thrombocytopenia (platelet count <150 K). Diabetes was defined by a physician note, self-reported medical history, or taking antidiabetic medication, or the American Diabetes Association criteria (fasting blood glucose $\geq$126 or glycated hemoglobin [HbA1c] >6.5\% or random glucose of 200 mg/dL with presence of symptoms). Exclusion criteria were as follows:

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Potential conflict of interest: Nothing to report.
Concurrent history of statin use was also abstracted. Information was obtained from the medication list and physician's notes. Reasons for stopping metformin were ascertained from the medication list and physician's notes. Concurrent history of statin use was also abstracted.

Clinical Information. Demographics, clinical information, and laboratory results at the time of cirrhosis diagnosis were abstracted from the electronic medical record, including age, gender, ethnicity, body mass index (BMI), etiology of cirrhosis, liver biochemistries, HbA1c, and plasma glucose level. Model for End-Stage Liver Disease (MELD) and Child-Pugh score, alpha-fetoprotein (AFP), the last follow-up date with vital status, and cause of death. The use of metformin and reasons for stopping metformin were ascertained from the medication list and physician's notes. Concurrent history of statin use was also abstracted.

Obesity was defined as BMI \( \geq 30 \) kg/m\(^2\). The etiology of cirrhosis was classified as NASH, alcoholic liver disease (ALD), hepatitis B virus (HBV) and HCV infection, and others (i.e., primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, hereditary hemochromatosis, Wilson's disease, alpha 1 antitrypsin deficiency, and cardiac cirrhosis). NASH was considered a cause of cirrhosis if there was a documented history of NASH or radiographic or histological evidence of fatty infiltration in the absence of a history of significant alcohol use. HBV infection was defined as a positive hepatitis B surface antigen, and HCV infection was defined as a positive HCV RNA. A diagnosis of HBV or HCV infection in the physician's note was accepted as a diagnosis of viral infection. Alcoholic cirrhosis was defined as having a documented history of ALD, alcohol abuse, or dependence or having alcohol greater than 140 and 70 g/week in men and women, respectively, and without other specific causes of cirrhosis.

Statistical Analysis. Baseline characteristics of patients who continued metformin versus discontinued metformin after cirrhosis diagnosis were compared using the Student t test for continuous variables and the chi-square test for categorical variables. Survival of patients in both groups was estimated using Kaplan-Meier's method and compared using the log-rank test. Survival time was calculated from the date of cirrhosis diagnosis to the date of last follow-up or death. Associations between predictor variables and survival were determined by HR and 95% confidence interval (CI) calculated using Cox proportional hazards regression. Variables with \( P \leq 0.1 \) in the univariate model were included in the multivariate model. MELD score was included in the multivariate analysis to adjust for the potential confounding effect of liver function. Individual components of the MELD score were not included in the multivariate analysis.

Results

Baseline Patient Characteristics. Of the total of 250 diabetic patients who were on metformin at the time of cirrhosis diagnosis, 142 (56.8%) were male with a mean age (± standard deviation [SD]) of 61.2 ± 9.8 years and 181 (73.3%) had Child-Pugh class A cirrhosis. The etiologies of cirrhosis were NASH (56.8%), ALD (11.6%), HCV (12.0%), HBV (2.4%), others (5.6%), and unknown (11.6%). Of the 250 diabetic patients on metformin at the time of cirrhosis diagnosis, 172 (68.8%) continued metformin whereas 78 (31.2%) discontinued metformin. Reasons for discontinuation of metformin included diagnosis of cirrhosis (\( n = 61 \); 78% of patients who discontinued metformin), uncontrolled plasma glucose (\( n = 5 \)), elevated serum creatinine (\( n = 3 \)), diarrhea (\( n = 2 \)), well-controlled plasma glucose level (\( n = 2 \)), switching to insulin therapy (\( n = 2 \)), unstated reasons during hospitalization (\( n = 2 \)), and heart disease (\( n = 1 \)).

Table 1 summarizes patient demographics and baseline characteristics of the continued and discontinued metformin groups. Age, gender, ethnicity, etiology of cirrhosis, BMI, ALT, prothrombin time (PT), international normalized ratio (INR), AFP, and severity of diabetes, as determined by HbA1c levels and fasting plasma glucose levels, were not significantly different between the two groups. Not surprisingly, the continued metformin group had significantly better liver function, demonstrated by a higher proportion of Child A patients with cirrhosis, and a lower MELD score (\( P = 0.01 \) and <0.001, respectively); thus, the potential effect of MELD score on outcome was assessed in subsequent analyses. Given that both MELD score and Child-Pugh classification reflect severity of liver impairment, we selected MELD score in the multivariate analysis because MELD score better correlates with severity of liver impairment than the Child-Pugh classification.

It has been reported that other medications, such as statins, may also benefit patients with cirrhosis. In an attempt to determine the effect of statins on survival, we compared the concurrent or previous use of statins in the cohort patients. The numbers of patients with a history of statin use who continued versus
discontinued metformin were 29 (16.9%) versus 9 (11.5%), respectively ($P = 0.27$). Thus, no significant difference was found in the frequency of statin use between the two groups.

**Survival of Patients Who Continued Metformin Versus Those Who Discontinued Metformin After Cirrhosis Diagnosis.** The median survival of patients who continued metformin was significantly greater than that of patients who discontinued metformin after cirrhosis diagnosis (11.8 vs. 5.6 years; $P < 0.0001$; Fig. 1). Five- and ten-year survival rates of patients who continued metformin versus those who discontinued metformin were 77.5% versus 53.1% and 55.2% versus 30.7%, respectively. The median time of metformin use in the continued metformin group was 26.8 months (range, 3.1-151.1). Therefore, most patients who continued metformin received metformin for substantially longer than 3 months, with 121 of the 172 (70.3%) receiving metformin for over 1 year (Supporting Fig. 1). In a sensitivity analysis to confirm that the 3 month cutoff did not overestimate

![Fig. 1. Survival of 250 diabetic patients who continued metformin versus those who discontinued metformin after cirrhosis diagnosis.](image-url)
the benefit of continuation of metformin, we com-
pared the survival of the diabetic patients who contin-
ued (n = 121) versus discontinued metformin (n = 129) 1 year after cirrhosis diagnosis. The median sur-
vival of the patients who continued metformin
remained significantly greater than that of the patients
who discontinued metformin within 1 year after cir-
rhosis diagnosis (11.8 vs. 6.0 years; P < 0.0001; Sup-
porting Fig. 2).

The benefit of continuation of metformin on sur-
vival was found regardless of severity of cirrhosis, as
defined by Child-Pugh classification. Of the 181 Child
A patients with cirrhosis, those who continued metfor-
mmin (n = 133) had a significantly greater median sur-
vival than those who discontinued metformin (n =
48; 11.8 vs. 6.0 years; P = 0.006) with an HR of 0.47
(95% CI: 0.27-0.82; P = 0.009; Fig. 2A). Similarly, in a pooled analysis, Child B (n = 61) and C (n = 5) patients with cirrhosis who continued metformin (n = 36) had a significantly greater median survival than those who discontinued metformin (n =
30; 7.7 vs. 3.5 years; P = 0.04) with an HR of 0.46
(95% CI: 0.21-0.98; P = 0.04; Fig. 2B).

When patients were categorized based on the etio-
logy of cirrhosis, the beneficial effect of metformin on
survival was observed only in the NASH-related cir-
rhosis group. The median survival of patients with
NASH-related cirrhosis who continued metformin (n =
98) versus discontinued metformin (n = 44) was
12.1 versus 5.1 years (P = 0.0004) with an HR of 0.33
(95% CI: 0.17-0.63; P < 0.0001; Fig. 3A). Sur-
vival of those who continued versus those who discon-
tinued metformin was not statistically different in the
alcohol-, HCV-, and HBV-related cirrhosis groups,
likely a result of the small number of patients in each
group (29, 30, and 6 patients, respectively). Thus, to
obtain a larger number, we combined patients with
cirrhosis from alcohol, HCV, HBV, other, and
unknown etiologies into a non-NASH cirrhosis group
(n = 108); no significant difference was observed in
survival between the continued metformin and discon-
tinued metformin subgroups (Fig. 3B).
Eighty-one patients (43 of 172 [25%] in the continued metformin group and 38 of 78 [49%] in the discontinued group) died during a median follow-up time of 5.2 years (range, 0.6-14.6). The median durations of follow-up were 4.8 (range, 0.6-14.6) and 5.4 years (range, 0.6-13.6) in the continued and discontinued groups, respectively. At the last follow-up visit, 129 (75%) and 40 (51%) patients in the continued and discontinued groups were alive, of whom 54 (41.9%) and 15 (37.5%) patients had been followed for at least 5 years, respectively. Of the 81 deceased patients, 39 (48%) had information on causes of death available in the medical record (21 and 18 in the continued and discontinued metformin groups, respectively). The causes of death included liver-related deaths (n = 32; 82% of those with available cause of death information), pulmonary disease (n = 3), and heart disease, renal failure, accident, and leukemia (n = 1 for each).

**Predictors of Survival of Patients With Cirrhosis With Diabetes.** Continuation of metformin use was significantly associated with better survival in patients with cirrhosis with diabetes. In univariate analysis, continuation of metformin (HR, 0.43; 95% CI: 0.28-0.66; P = 0.0001) and high serum albumin level (HR, 0.53; 95% CI: 0.36-0.77; P = 0.001) were significantly associated with better survival. By contrast, every 10-year increase in age (HR, 1.59; 95% CI: 1.25-2.02; P = 0.0001), male sex (HR, 1.77; 95% CI: 1.11-2.82; P = 0.02), increased MELD score (HR, 1.08; 95% CI: 1.02-1.13; P = 0.007), loge bilirubin (HR, 1.39; 95% CI: 1.07-1.82; P = 0.015), serum creatinine (HR, 2.7; 95% CI: 1.51-4.87; P = 0.0009), and every 10-ng/mL increase in serum AFP value (HR, 1.13; 95% CI: 1.09-1.17; P < 0.0001) were significantly associated with worse survival. Etiology of cirrhosis was also associated with survival; compared to the reference group with HBV-induced cirrhosis, patients with HCV, NASH, or other causes of cirrhosis had HRs in the 1.3-1.5 range, whereas those with cirrhosis resulting from ALD had an HR of 3.8; however, none of these associations was statistically significant. Ethnicity, ALT, platelet count, INR, PT, and fasting plasma glucose were not associated with survival (Table 2).

The benefit of metformin use on survival outcome remained significant after adjusting for other variables (i.e., age, gender, albumin, MELD score, AFP level, and etiology of cirrhosis; Table 2). Continuation of metformin use was independently associated with a 57% decrease in the risk of death with a HR of 0.43 (95% CI: 0.24-0.78; P = 0.005). By contrast, every 10-ng/mL increase in AFP value was associated with a 13% increased risk for mortality (HR, 1.13; 95% CI: 1.07-1.18; P < 0.0001; Table 2). Given that the information on AFP value was missing in 52 of 250 (20.8%) patients, we also performed another multivariate analysis excluding the AFP value, and the primary finding of an association between the continuation of metformin use and survival remained unchanged (HR, 0.38; 95% CI: 0.23-0.64; P = 0.0002; Supporting Table 1).

**Discussion**

We conducted a clinic-/hospital-based cohort study to determine the outcomes and safety of metformin in diabetic patients with cirrhosis. Continuation of metformin use after cirrhosis diagnosis was associated with significantly improved survival in diabetic patients, regardless of severity of liver impairment. Our data suggest that metformin is safe in diabetic patients with cirrhosis because no patients developed lactic acidosis while receiving metformin in our cohort.

In this study, metformin use was significantly associated with a 57% reduction in risk of all-cause mortality in diabetic patients with all stages of cirrhosis. Our finding suggested that metformin may prevent liver-related mortality because most patients (82%) died from liver-related diseases. The mechanism by which metformin reduces mortality in patients with cirrhosis is currently unknown. Given that metformin use had a protective effect against death only in the subgroup of NASH-related patients with cirrhosis, it is biologically plausible that metformin may slow progression of liver fibrosis by attenuating steatohepatitis. This hypothesis is supported by evidence from recent studies. Metformin has been demonstrated to reverse steatosis and inflammation in a mouse model with NASH, reduce hepatocellular injury and improve ALT levels in NASH patients, and significantly decrease hepatic fat, necroinflammation, and fibrosis in nondiabetic NASH patients.

We did not find a significant survival benefit in subgroups of patients with cirrhosis induced by HCV, HBV, or alcohol, possibly because of the small numbers of patients, or the entire group of patients with non-NASH-induced cirrhosis. Additional studies in larger cohorts are needed to determine whether metformin confers a survival benefit for diabetic patients with cirrhosis from causes other than NASH.

Baseline liver function, as indicated by MELD score and Child-Pugh classification, is known to be a strong predictor of survival in patients with cirrhosis. In our study, MELD score was not associated with survival of patients with cirrhosis, likely because most patients had low MELD scores. We found that a significantly
higher proportion of patients continuing metformin had Child-Pugh class A cirrhosis and a lower mean MELD score than those who discontinued metformin. To determine whether baseline liver function confounds the association of metformin continuation and survival, we adjusted for the MELD score in the multivariate analysis. Metformin continuation remained a significant predictor of better survival after adjusting for the MELD score. In addition, we also categorized patients based on Child-Pugh classification and determined the effect of metformin on survival of patients with Child-Pugh class A versus Child-Pugh class B/C cirrhosis separately. There was a significant benefit of metformin continuation in both the Child-Pugh class A and B/C cirrhosis groups. This suggests that metformin can be continued in diabetic patients with compensated or decompensated cirrhosis, if there is no specific contraindication.

Although the main reason for discontinuation of metformin in our cohort was the concern about an increased risk of developing lactic acidosis, no patient developed lactic acidosis or serious complications from metformin use. In fact, the incidence of lactic acidosis in diabetic patients on metformin is extremely low.21-23 Specifically, most patients who developed metformin-induced lactic acidosis had risk factors for lactic acidosis, particularly, marked renal impairment.25 Preexisting renal insufficiency and cardiac disease (e.g., heart failure) have been commonly reported as risk factors for metformin-induced lactic acidosis, whereas liver impairment was rarely identified as a risk factor for lactic acidosis.25-27 Indeed, despite the widespread use of metformin, very few cases with preexisting liver impairment have been reported to develop lactic acidosis (2 with cirrhosis,28 1 actively drinking alcoholic patient with cirrhosis,24 and 1 with liver failure).25 Thus far, no studies have specifically determined the incidence of lactic acidosis in a cohort of patients with cirrhosis on metformin. Interestingly, none of the Child B (n = 33; 19.5%) and C (n = 3; 1.8%) patients in our cohort experienced a life-threatening complication resulting from the use of metformin. Thus, our data, albeit with a small number of decompensated patients with cirrhosis, suggested the safety of metformin use in patients with cirrhosis without a specific contraindication.

Controlling blood sugar in diabetic patients with cirrhosis can be more challenging because of

Table 2. Cox Proportional Hazards Analysis of Variables Associated With Death of Patients With Cirrhosis With Diabetes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td>Adjusted HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age, per 10 years</td>
<td>1.59 (1.25-2.02)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>1.77 (1.11-2.82)</td>
<td>0.02</td>
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<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>1.00 (reference)</td>
<td>0.10</td>
</tr>
<tr>
<td>White</td>
<td>2.33 (0.85-6.40)</td>
<td>0.10</td>
</tr>
<tr>
<td>BMI</td>
<td>0.25 (0.04-1.54)</td>
<td>0.14</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.35 (0.85-2.10)</td>
<td>0.20</td>
</tr>
<tr>
<td>Etiology of cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>HCV</td>
<td>1.37 (0.17-10.77)</td>
<td>0.39 (0.04-3.52)</td>
</tr>
<tr>
<td>ALD</td>
<td>3.86 (0.51-29.25)</td>
<td>2.29 (0.29-18.27)</td>
</tr>
<tr>
<td>NASH</td>
<td>1.32 (0.18-9.69)</td>
<td>0.97 (0.13-7.53)</td>
</tr>
<tr>
<td>Others</td>
<td>1.42 (0.16-12.77)</td>
<td>0.71 (0.07-7.57)</td>
</tr>
<tr>
<td>MELD score</td>
<td>1.08 (1.02-1.13)</td>
<td>0.0067</td>
</tr>
<tr>
<td>Laboratory results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST level</td>
<td>1.0 (0.99-1.004)</td>
<td>0.97</td>
</tr>
<tr>
<td>ALT level</td>
<td>0.998 (0.994-1.002)</td>
<td>0.41</td>
</tr>
<tr>
<td>Loge bilirubin</td>
<td>1.39 (1.07-1.82)</td>
<td>0.015</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.53 (0.36-0.77)</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelets</td>
<td>1.001 (0.998-1.004)</td>
<td>0.56</td>
</tr>
<tr>
<td>INR</td>
<td>1.27 (0.54-2.98)</td>
<td>0.59</td>
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<tr>
<td>Creatinine</td>
<td>2.70 (1.51-4.87)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Fasting plasma glucose,</td>
<td>0.998 (0.994-1.003)</td>
<td>0.47</td>
</tr>
<tr>
<td>AFP, per 10 ng/mL†</td>
<td>1.13 (1.09-1.17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Continuing metformin after cirrhosis diagnosis</td>
<td>0.43 (0.28-0.66)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* MELD was included in this model rather than bilirubin, INR, and creatinine.
† AFP of >200 ng/mL was coded as 200 ng/mL.
Abbreviation: AST, aspartate aminotransferase.
fluctuations in blood sugar levels; hypoglycemia is a particular concern of physicians when prescribing oral hypoglycemic agents. Therefore, some physicians prefer insulin to avoid hypoglycemia in diabetic patients with cirrhosis. However, metformin does not cause hypoglycemia and can be used in combination with insulin without increasing the risk of hypoglycemia.

Interestingly, AFP was an independent risk factor for death of patients with cirrhosis with diabetes. Given that a rising AFP value is used as a predictor of HCC development, we investigated whether metformin decreased the risk of HCC development in our cohort. We did not find a significant association between continuation of metformin and reduced HCC risk (data not shown). This result was inconsistent with the study by Chen et al., which reported that metformin reduced risk of HCC development by 7% per year. This inconsistency may result from the limited number of patients who developed HCC in our cohort (n = 10 [5.8%] in continued and 5 [6.4%] in discontinued groups), because this cohort study was powered to address the difference in survival, instead of HCC incidence, in the patients with cirrhosis. The information on lack of apparent HCC risk reduction was provided as an underpowered secondary analysis.

The major strength of our study lies in the large cohort of patients with cirrhosis with diabetes who have various causes of cirrhosis and a wide range of degrees of severity of liver impairment. To our knowledge, this is the largest cohort of unselected patients with cirrhosis with diabetes in which the effect of metformin use has been investigated. We also provided data on the safety of metformin use in patients with cirrhosis. Therefore, this study has contributed significantly to filling the knowledge gap in the debate on whether metformin can be safely prescribed to patients with cirrhosis. Importantly, our study revealed the novel observation of an association between metformin use and improved survival in a cohort of patients with cirrhosis with diabetes.

Our study had a number of limitations. We were not able to take into consideration the effect of dose or duration of metformin treatment on survival. Because of the retrospective study design, detailed information on use of antidiabetic agents was not always available. Thus, we were not able to determine the minimum effective dose of metformin that resulted in improved survival of patients with cirrhosis. Metformin is the major antidiabetic agent with a biologically plausible mechanism for improving liver function. Other medications may also benefit patients with cirrhosis; however, the sample size of the study was not large enough to sustain the multivariate model that would be needed to investigate the effect of metformin and, at the same time, provide valid estimates of the concomitant effects of other medications. We were not able to confirm a benefit of metformin use on reducing HCC incidence as a result of the limited number of patients who developed HCC in our cohort. Moreover, although we adjusted for MELD score to account for the influence of more-severe comorbidities in the decision to discontinue metformin, MELD score may not completely account for the effects of all possible comorbidities.

A number of research questions should be further investigated. It is worth examining the effect of metformin on survival of patients with non-NASH cirrhosis in a larger cohort. Whether initiating metformin subsequent to diagnosis of cirrhosis would improve survival of diabetic patients needs to be answered. It will also be interesting to further investigate whether metformin has an antifibrotic effect by slowing down progression or reversing the degree of liver fibrosis. Given that the prevalence of impaired glucose tolerance in patients with cirrhosis is as high as 50%-60%, it will be of interest to investigate whether metformin also improves the outcomes of patients with cirrhosis with impaired glucose tolerance.

In conclusion, we report on the novel observation of an association between continuation of metformin use after cirrhosis diagnosis and improved survival of diabetic patients. Our findings strongly suggest that continuation of metformin improves the survival of NASH-related patients with cirrhosis with diabetes. Validation of these results in a larger cohort would support continuation of metformin use in NASH-related cirrhosis.

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References


Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.27199/suppinfo.