Independent and Joint Use of Statins and Metformin by Elderly Patients With Diabetes and Overall Survival Following HCC Diagnosis

Samuel O. Antwi, PhD,* Zhuo Li, MS,* Kabir Mody, MD,†
Lewis R. Roberts, MB, ChB, PhD,‡ and Tushar Patel, MB, ChB§

Goal: To investigate associations of prediagnosis and postdiagnosis use of statins and metformin on overall survival of patients with diabetes who later developed HCC.

Background: Statins and metformin have received considerable interest as potential chemopreventive agents against hepatocellular carcinoma (HCC) development in individuals with type 2 diabetes mellitus (T2DM); however, their impact on overall survival of patients with T2DM who later develop HCC (diabetic HCC patients) is unclear.

Study: Data on 2499 elderly diabetic HCC patients obtained from the SEER-Medicare program (2009 to 2013) were analyzed. Patients were categorized based on use of statins only, metformin only, both, or neither (reference for all comparisons). The patients were further categorized based on: (1) metformin dose: ≤ 1500 or > 1500 mg/d; (2) statins functional form: hydrophilic (pravastatin and rosuvastatin) or lipophilic (atorvastatin, fluvastatin, lovastatin, and simvastatin); (3) statins potency: high (atorvastatin, rosuvastatin, and simvastatin) or low (fluvastatin, lovastatin, and pravastatin); and (4) individual statins type. Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CIs) were calculated using Cox proportional hazard models.

Results: Prediagnosis use of metformin dose ≤ 1500 mg/d was associated with lower risk of death after HCC diagnosis in patients with T2DM (HR, 0.72; 95% CI, 0.58-0.91), adjusting for post-diagnosis metformin dose, diabetes severity, Charlson comorbidity index, tumor characteristics, and other relevant factors. No association was found for prediagnosis metformin dose > 1500 mg/d or post-diagnosis metformin use. Further, no association was found for either prediagnosis or postdiagnosis statins use.

Conclusions: Prediagnosis use of metformin dose ≤ 1500 mg/d is associated with longer overall survival of elderly diabetic HCC patients.

Key Words: liver cancer, hepatocellular cancer, HCC, statins, metformin

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Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and accounts for about 80% of all liver cancer diagnoses worldwide.[1] In the United States, liver cancers, including HCC and the less common cholangiocarcinoma, are projected to become the third leading cause of cancer death by 2030.[2] Major risk factors for HCC include chronic hepatitis C virus (HCV) and hepatitis B virus (HBV) infections, alcoholic liver disease and metabolic disorders, such as type 2 diabetes mellitus (T2DM) and metabolic syndrome.[3] HCC currently has a 5-year survival rate of 18%, which is due mostly to delayed diagnosis.[4] When diagnosed at an early stage, HCC is often treated with surgical resection, liver transplantation, or radiofrequency ablation, all of which are associated with improved prognosis. Systemic medications, such as sorafenib, regorafenib, and niolumab, have also shown some modest benefits for management of advanced HCC.[5–7] However, there remains a pressing need to identify modifiable factors that can help further prolong survival of HCC patients.

T2DM is a global epidemic.[8] Incidence of T2DM has been increasing in the United States in parallel with the increasing incidence of obesity.[8,9] Many patients with T2DM develop HCC after the diagnosis of T2DM (diabetic HCC patients),[10,11] and preexisting T2DM is now recognized as not just a risk factor for HCC but also an independent predictor of shorter survival after diagnosis of HCC.[12] T2DM is often managed with metformin, a first-line oral antihyperglycemic agent. Studies have shown that metformin is commonly taken simultaneously with statins (cholesterol lowering medications) because most patients with T2DM have also hyperlipidemia.[13,14] Experimental studies suggest that both statins and metformin may have therapeutic potential for prolonging survival of HCC patients.[15,16] The proposed mechanisms for the role of statins in cancer survival include cell-cycle arrest, apoptosis induction, and posttranslational modification of RAS proteins.[17–19] Postulated anticancer effects of metformin also include attenuation of metabolic abnormalities[20] and suppression of the mammalian target of rapamycin (mTOR) signaling pathway that is known to enhance cancer cell proliferation.[21–23] However, findings from epidemiologic association studies are mixed.[24–27]

At least 2 epidemiological studies have examined the association between use of statins and overall survival of HCC patients and have reported conflicting results.[24,25] The same is the case for metformin, with at least 2 studies reporting a beneficial association[26,27] and one study reporting a null association.[28] Although many patients taking metformin for T2DM take also statins for hyperlipidemia,[29] none of the existing studies examined associations for combined use of statins and metformin on overall survival of diabetic HCC patients. In addition, no study has examined associations for prediagnosis and postdiagnosis use of statins or metformin while adjusting for the effect of the other. Prediagnosis and postdiagnosis statins or metformin use may have differential

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association with survival in HCC patients, as seen in other malignancies.[30] These gaps in knowledge necessitate further investigations to delineate the roles of statins and metformin in survival of diabetic HCC patients. We, therefore, investigated associations of prediagnosis and postdiagnosis use of statins and metformin, both independently and jointly, on overall survival after HCC diagnosis in a nationally representative sample of elderly patients with T2DM using data from the Surveillance, Epidemiology, and End Results (SEER) registry linked to Medicare claims information (SEER-Medicare).

MATERIAL AND METHODS

Data Source and Study Population

Following approval by the Mayo Clinic Institutional Review Board (IRB), we obtained data from the SEER-Medicare program. A detail description of the SEER-Medicare program has been provided.[31] In brief, the SEER program is supported by the National Cancer Institute and includes data collected from population-based cancer registries that cover 18 geographic regions: Atlanta, GA; Connecticut; Detroit, MI; Hawaii; Iowa; New Mexico; San Francisco-Oakland, CA; Seattle-Puget Sound, Seattle, WA; Utah; Los Angeles, CA; San Jose-Monterey, CA; Rural Georgia; Alaska; Greater California; Greater Georgia; Kentucky; Louisiana; and New Jersey. The Medicare program provides payments for hospital, physician, and outpatient medical services for about 97% of US citizens of age 65 years or older.[31] Data on cancer patients reported to SEER who are 65 years or older are linked to Medicare claims data of the respective patients for SEER-Medicare studies. The areas covered by the SEER-Medicare program represents about 25% of the general US population.[31] The Medicare claims files include information on medical diagnosis, medical procedures, and prescription drug claims. The Medicare Part A file contains claims for hospital, skilled nursing facility, and hospice services. The Medicare Part B file covers claims for physician and outpatient services, and the Medicare Part D file covers prescription drug claims. As of June 2018, data on SEER-Medicare Parts A and B were available through December 2014. Complete data on Medicare Part D prescription drug coverage were available from 2008 to 2013. To allow for a 1-year window for assessment of baseline comorbidities and utilization of Medicare Part D prescription drug coverage, analyses were restricted to patients diagnosed with HCC from January 1, 2009 to December 31, 2013. The *International Classification of Disease, Ninth Revision* (ICD-9) code 250.xx was used to identify patients with T2DM in the SEER-Medicare data, following which the *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) topography code C22.0 was used to identify the T2DM cases with diagnosis of liver cancer. We then used the *International Classification of Diseases for Oncology, Third revision* (ICD-O-3) histologic codes 8170 to 8174 to subset to the liver cancers to HCC only. The HCC diagnosis date had to have occurred after T2DM diagnosis date for inclusion in the study. Details of the sample selection process are provided in Figure 1. In Brief, we identified 9204 patients with T2DM with first primary histologically-confirmed HCC diagnosed between January 1, 2009 and December 31, 2013. We then excluded patients co-enrolled in Medicare and Private Health Maintenance Organizations (n = 778) and those who were not continuously enrolled in Medicare Parts A and B in the 12 months preceding HCC diagnosis
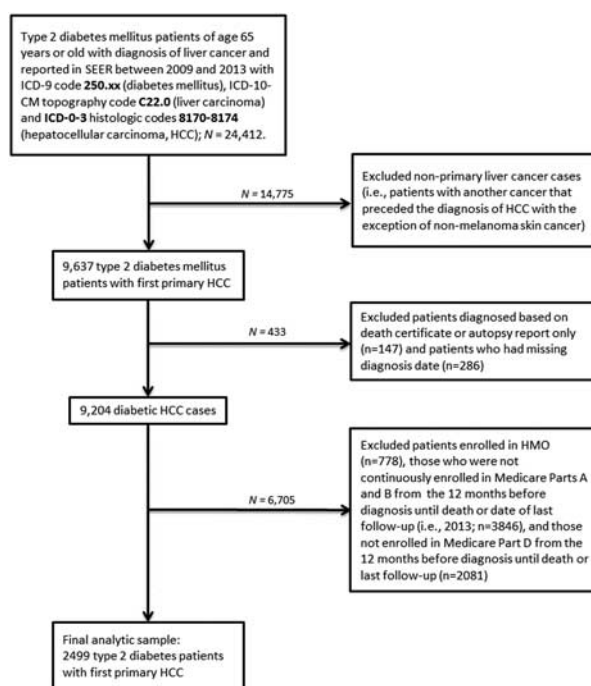

FIGURE 1. Flow chart of study sample selection process.

until death or last follow-up (n = 3846). We further excluded patients not enrolled in Medicare Part D prescription drug coverage in the 12 months before diagnosis until death or last follow-up (n = 2081), leaving a final sample of 2499 patients with T2DM and incident HCC for analyses (Fig. 1).

Sociodemographic Information, Clinic Characteristics, and Outcome Variable

Sociodemographic information, including age, sex, race/ethnicity, marital status, body mass index (BMI), neighborhood level income, and percentage of persons with a 4-year college education in neighborhood were abstracted from the Patient Entitlement and Diagnosis Summary File (PEDSF). Information on tumor characteristics, including stage, grade and size were obtained from the SEER file. Data on comorbid conditions (eg, cardiovascular disease, diabetes, HBV, and HCV) were identified using ICD-9 codes from the PEDSF, the Medicare Provider Analysis and Review (MEDPAR), Carrier data, and Outpatient Standard Analytical File. Comorbidities had to have existed at least 1-year before HCC diagnosis and we calculated the Charlson comorbidity index, as described.[32] Because all participants had diagnosis of T2DM, we further calculated diabetes severity index as described in detail by Young et al.[33] Data on cancer treatment received by the patients were derived from the Medicare Provider Analysis and Review, the Carrier, the Outpatient, and the Standard Analytical Files using ICD-9 codes. The outcome of interest was overall survival. Survival time was calculated as the number of completed months from the date of diagnosis to the date of death, date last known to be alive, or date of last follow-up (December 31, 2013), whichever occurs first. Individuals who were alive at the end of follow-up were censored at that time.

Statins and Metformin Use

Data on statins and metformin use were abstracted from the Medicare Part D prescription drug file. Statins and metformin use before and after diagnosis of HCC were determined by comparing the prescription date to the date of HCC diagnosis. Prediagnosis medication use was defined as medication use initiated at least a year before HCC diagnosis and postdiagnosis medication use defined as medication use initiated at least one day after diagnosis. Medication use was initially categorized as statins only, metformin only, both statins and metformin, or neither. Average daily metformin dose was calculated as the total milligrams of metformin dispensed divided by the total number of days of prescription and metformin users were categorized into ≤ 1500 mg/dy or > 1500 mg/d.[34] Statins users were categorized further based on (1) the functional form of the statins: hydrophilic (pravastatin and rosuvastatin) or lipophilic (atorvastatin, fluvastatin, lovastatin, and simvastatin),[35] (2) statins potency: high potency (atorvastatin, rosuvastatin, and simvastatin) or low potency (fluvastatin, lovastatin, and pravastatin),[36] and (3) the individual statins types.

Statistical Analysis

Distributions of sociodemographic and clinical characteristics of the participants were compared by prediagnosis use of statins only, metformin only, both, or neither, using χ^2 tests for categorical variables and Student *t* test for continuous variables. Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Before fitting the Cox proportional models, the proportional hazard assumption was assessed by creating interaction variables between the predictors and a log transformation of survival time[37] and was determined to have been satisfied. Association analyses were performed in minimally adjusted and fully adjusted models. The minimally adjusted model included age, sex, and prediagnosis and postdiagnosis medication use. In the fully adjusted model, additional adjustment for year of diagnosis, race/ethnicity, marital status, neighborhood income level, percent with 4-year college in neighborhood, tumor grade, tumor stage, chemotherapy, radiation, Charlson comorbidity index, diabetes severity index, obesity, presence of chronic obstructive pulmonary disease (COPD), dyslipidemia, and hepatitis status (HBV, HCV, both, none) were performed as categorized in Table 1. Associations for prediagnosis and postdiagnosis medication use were initially assessed among users of statins only, metformin only, both, and neither (ie, nonusers; reference group). Associations for use of prediagnosis and postdiagnosis hydrophilic and lipophilic statins and for use of high or low potency statins were assessed compared with nonusers. We assessed also associations for individual statins type (pravastatin, rosuvastatin, atorvastatin, fluvastatin, lovastatin, and simvastatin) compared with nonusers. Finally, we examined associations for average daily metformin dose (≤ 1500 mg/d, > 1500 mg/d vs. nonusers) used prediagnosis and postdiagnosis of HCC. All statistical tests were 2-sided and a *P*-value < 0.05 was considered statistically significant. Analyses were performed in SAS® version 9.4 (SAS Institute, Cary, NC).

RESULTS

Descriptive characteristics of the study participants, including age, marital status, and HCC tumor stage, grade and size, were examined among prediagnosis users of statins only, metformin only, both statins and metformin, and nonusers (Table 1). The statins only users were slightly older (mean age, 77 y) and included a higher proportion of non-Hispanic Whites (58%) than users of metformin only (mean age, 73 y; 55% non-Hispanic Whites), both statins and metformin (mean age, 76 y; 56 non-Hispanic Whites), or nonusers (mean age, 75 y; 57% males). Users of both statins and metformin were more likely to present with stage III or IV HCC tumors (41%) compared with users of statins only (35%), metformin only (32%), and nonusers (30%). Statins only users were more likely to have larger tumors (ie, ≥ 5 cm; 53%) than users of metformin only (39%), both statins and metformin (50%), and nonusers (37%). In addition, users of both statins and metformin had higher Charlson comorbidity index, whereas users of statins only had higher diabetes severity index compared with the other groups, but no differences were observed by sex, marital status, neighborhood income or education level, tumor grade, or treatment with chemotherapy or radiation. Other findings are reported in Table 1.

Median survival in the entire population was 9.2 months; it was highest among nonusers (10.7 mo), followed by prediagnosis users of metformin only (9.5 mo), both metformin and statins (8.0 mo), and lowest among statins only users (7.1 mo). Results for associations of statins and/or metformin use and overall survival after HCC diagnosis did not show any significant association for either prediagnosis or postdiagnosis use of statins only, metformin only, or both when compared with nonusers (Fig. 2). Kaplan-Meier survival curves for prediagnosis use of statins only, metformin only, both statins and metformin, and nonuse did not show any differences in overall survival across follow-up (Log-rank *P*-value = 0.06) (Fig. 3).

We evaluated additional details about statins and metformin use regarding functional form of the statins, statins potency, and average daily dose of metformin (Fig. 4). In the fully adjusted model that included adjustment for postdiagnosis metformin dose, prediagnosis average daily metformin dose ≤ 1500 mg was associated with a 28% lower risk of death after HCC diagnosis (HR, 0.72; 95% CI, 0.58-0.91; ≤ 1500 mg/d vs. nonusers). By contrast, average prediagnosis metformin dose in excess of 1500 mg/d was not associated with survival after HCC diagnosis (HR, 0.98; 95% CI, 0.86-1.11; > 1500 mg/d vs. nonusers), after adjusting for prost-diagnosis metformin dose and other covariates. Similarly, no association was found for either prediagnosis or postdiagnosis statins form, statins potency, or postdiagnosis metformin dose (Figs. 4, 5). We further examined associations for individual statins type used either prediagnosis or postdiagnosis of HCC and no association was found for any of the individual statins type (Fig. 6).

DISCUSSION

In this population-based study of elderly patients with diabetes, we examined associations of independent and joint use of statins and metformin both prediagnosis and postdiagnosis of HCC on overall survival. The results show that prediagnosis use of average daily metformin dose ≤ 1500 mg is associated with a 28% lower risk of death after HCC diagnosis in T2DM patients. No associations was found for prediagnosis metformin dose > 1500 mg/d or postdiagnosis metformin use, irrespective of dose. Prediagnosis and postdiagnosis use of statins also was not associated with risk of

TABLE 1. Demographic and Clinical Characteristics of Diabetic HCC Patients by Prediagnostic Statin and/or Metformin Use Groups (*N* = 2499)

Patient Characteristics	Nonusers (N = 1193)	Statins Only (N = 582)	Metformin Only (N = 295)	Both (N = 429)	P
Age at diagnosis (y)					< 0.0001
N	1193	582	295	429	
Mean (SD)	75.0 (7.2)	77.3 (6.7)	73.5 (6.3)	75.6 (6.1)	
Range	(65.0-100.0)	(65.0-94.0)	(65.0-96.0)	(65.0-94.0)	
Sex					0.0873
Male	717 (60.1)	384 (66.0)	185 (62.7)	276 (64.3)	
Female	476 (39.9)	198 (34.0)	110 (37.3)	153 (35.7)	
Marital status					0.1650
Married/cohabitation	542 (45.4)	287 (49.3)	144 (48.8)	216 (50.3)	
Separated/divorced/widowed	423 (35.5)	211 (36.3)	101 (34.2)	149 (34.7)	
Single	178 (14.9)	64 (11.0)	41 (13.9)	43 (10.0)	
Unknown	50 (4.2)	20 (3.4)	9 (3.1)	21 (4.9)	
Race					0.0023
Non-Hispanic White	676 (56.7)	335 (57.6)	163 (55.3)	240 (55.9)	
Non-Hispanic Black	125 (10.5)	57 (9.8)	24 (8.1)	24 (5.6)	
Asian	209 (17.5)	126 (21.6)	54 (18.3)	84 (19.6)	
Hispanic	93 (7.8)	35 (6.0)	36 (12.2)	48 (11.2)	
Unknown/other	90 (7.5)	29 (5.0)	18 (6.1)	33 (7.7)	
Neighborhood median income level					0.2888
< $35,000	378 (31.7)	177 (30.4)	91 (30.8)	119 (27.7)	
$35,000-49,000	292 (24.5)	117 (20.1)	64 (21.7)	93 (21.7)	
$50,000-74,999	181 (15.2)	105 (18.0)	55 (18.6)	82 (19.1)	
≥ 75,000	101 (8.5)	48 (8.2)	21 (7.1)	30 (7.0)	
Unknown	241 (20.2)	135 (23.2)	64 (21.7)	105 (24.5)	
Percent with 4-year college education in neighborhood					0.8009
< 10%	267 (22.4)	120 (20.6)	69 (23.4)	98 (22.8)	
10-19%	272 (22.8)	126 (21.6)	69 (23.4)	82 (19.1)	
20-29%	150 (12.6)	77 (13.2)	37 (12.5)	55 (12.8)	
≥ 30%	263 (22.0)	124 (21.3)	56 (19.0)	89 (20.7)	
Unknown	241 (20.2)	135 (23.2)	64 (21.7)	105 (24.5)	
Tumor grade					0.2243
I (well differentiated)	153 (12.8)	74 (12.7)	38 (12.9)	54 (12.6)	
II (moderately differentiated)	190 (15.9)	109 (18.7)	51 (17.3)	83 (19.3)	
III, IV (poorly differentiated)	82 (6.9)	56 (9.6)	22 (7.4)	54 (12.6)	
Unknown	768 (64.4)	343 (59.0)	184 (62.4)	238 (55.5)	
Stage					0.0008
Stage I	445 (37.3)	219 (37.6)	116 (39.3)	145 (33.8)	
Stage II	185 (15.5)	57 (9.8)	44 (14.9)	40 (9.3)	
Stage III, IV	209 (30.2)	123 (35.0)	58 (31.9)	109 (41.5)	
Unknown	202 (16.9)	102 (17.5)	38 (12.9)	66 (15.4)	
Tumor size					< 0.0001
< 5 cm	526 (44.1)	159 (27.3)	126 (42.7)	123 (28.7)	
≥ 5 cm	441 (37.0)	308 (52.9)	116 (39.3)	214 (49.9)	
Unknown	226 (18.9)	115 (19.8)	53 (18.0)	92 (21.4)	
Chemotherapy					0.5669
No	1102 (92.4)	542 (93.1)	274 (92.9)	405 (94.4)	
Yes	91 (7.6)	40 (6.9)	21 (7.1)	24 (5.6)	
Radiation					0.1299
No	996 (83.5)	493 (84.7)	254 (86.1)	378 (88.1)	
Yes	197 (16.5)	89 (15.3)	41 (13.9)	51 (11.9)	
Charlson comorbidity index score					< 0.0001
0	217 (18.2)	51 (8.8)	6 (2.0)	4 (0.9)	
1	258 (21.6)	88 (15.1)	48 (16.3)	83 (19.3)	
2	189 (15.8)	114 (19.6)	73 (24.7)	92 (21.4)	
3-5	411 (34.5)	236 (40.5)	124 (42.0)	177 (41.3)	
> 5	118 (9.9)	93 (16.0)	44 (14.9)	73 (17.0)	
Diabetes severity index					< 0.0001
0	227 (19.0)	70 (12.0)	61 (20.7)	69 (16.1)	
1	188 (15.8)	54 (9.3)	46 (15.6)	54 (12.6)	
2	293 (24.6)	88 (15.1)	46 (15.6)	48 (11.2)	
≥ 3	485 (40.7)	370 (63.6)	142 (48.1)	258 (60.1)	

TABLE 1. (*continued*)

	n (%)				
Patient Characteristics	**Nonusers (N = 1193)**	**Statins Only (N = 582)**	**Metformin Only (N = 295)**	**Both (N = 429)**	***P***
Obese (BMI $\geq 30\,kg/m^2$)					< 0.0001
No	1005 (84.2)	449 (77.1)	235 (79.7)	306 (71.3)	
Yes	188 (15.8)	133 (22.9)	60 (20.3)	123 (28.7)	
COPD					< 0.0001
No	699 (58.6)	286 (49.1)	193 (65.4)	259 (60.4)	
Yes	494 (41.4)	296 (50.9)	102 (34.6)	170 (39.6)	
Dyslipidemia					< 0.0001
No	483 (40.5)	49 (8.4)	98 (33.2)	28 (6.5)	
Yes	710 (59.5)	533 (91.6)	197 (66.8)	401 (93.5)	
Hepatitis type					< 0.0001
None	524 (43.9)	365 (62.7)	154 (52.2)	311 (72.5)	
Hepatitis B	23 (1.9)	8 (1.4)	4 (1.4)	8 (1.9)	
Hepatitis C	584 (49.0)	182 (31.3)	127 (43.1)	93 (21.7)	
Hepatitis B & C	48 (4.0)	17 (2.9)	7 (2.4)	13 (3.0)	
Unspecified type	14 (1.2)	10 (1.7)	3 (1.0)	4 (0.9)	

BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; HCC, hepatocellular carcinoma.

death in patients with T2DM after HCC diagnosis. In summary, the study suggests that prediagnosis metformin dose ≤ 1500 mg/d may improve survival of elderly diabetic HCC patients.

Metformin and statins are 2 of the most commonly prescribed medications among the elderly in the United States[13,14] and both have shown some promise for potential use as chemopreventive agents or adjuvant therapy for HCC.[38,39] Metformin is the most widely used oral hypoglycemic agent for treatment of T2DM.[13] In patients with T2DM, metformin improves insulin sensitivity, suppresses hepatic gluconeogenesis, and reduces glycogenolysis.[40] Preexisting T2DM is a known risk factor for HCC and associated with 2-fold to 4-fold increased risk for HCC.[10,41–43] In a case-control study of patients with diabetic, Donadon et al[43] reported an inverse association between metformin use and HCC risk. Nkontchou et al[44] also found inverse association between metformin use and risk for HCC in a prospective study of diabetics with HCV-induced
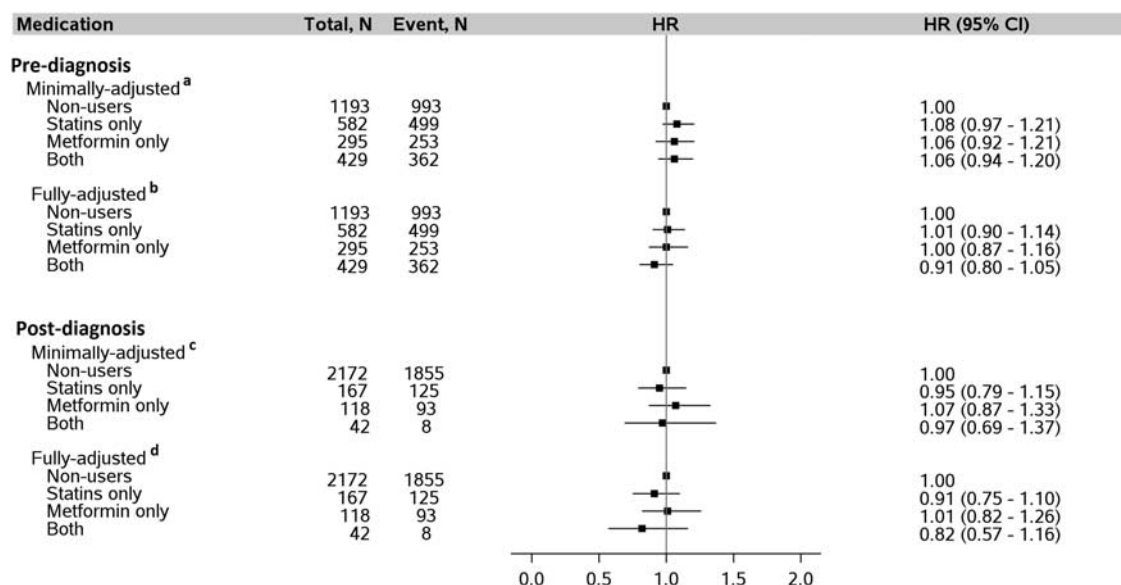
FIGURE 2. Association between use of statins and/or metformin by patients with diabetes prediagnosis and postdiagnosis of HCC and risk of death after HCC diagnosis. [a]Adjusted for age (continuous), sex, and postdiagnosis medication use (statins only, metformin only, both, neither). [b]Adjusted for everything in "a" plus year of diagnosis, race, marital status, neighborhood income level, percent with 4-year college in neighborhood, tumor grade, tumor stage, chemotherapy, radiation, Charlson comorbidity index, diabetes severity index, obesity, presence of COPD, dyslipidemia, and hepatitis as categorized in Table 1. [c]Adjusted for age, sex, and prediagnosis medication use (statins only, metformin only, both, neither). [d]Adjusted for everything in "c" with additional adjustment for year of diagnosis, race, marital status, neighborhood income level, percent with 4-year college in neighborhood, tumor grade, tumor stage, chemotherapy, radiation, Charlson comorbidity index, diabetes severity index, obesity, COPD, dyslipidemia, and hepatitis as categorized in Table 1. COPD indicates chronic obstructive pulmonary disease; HCC, hepatocellular carcinoma.
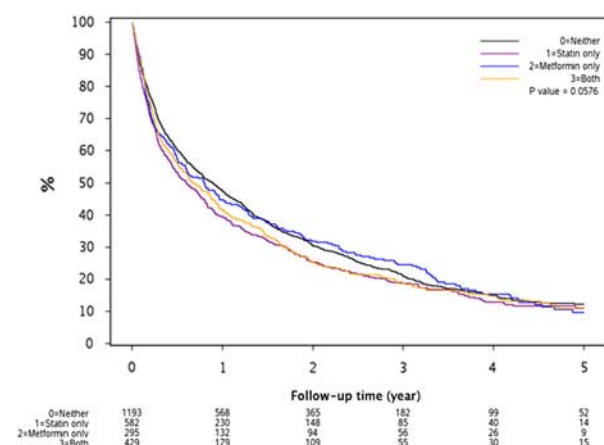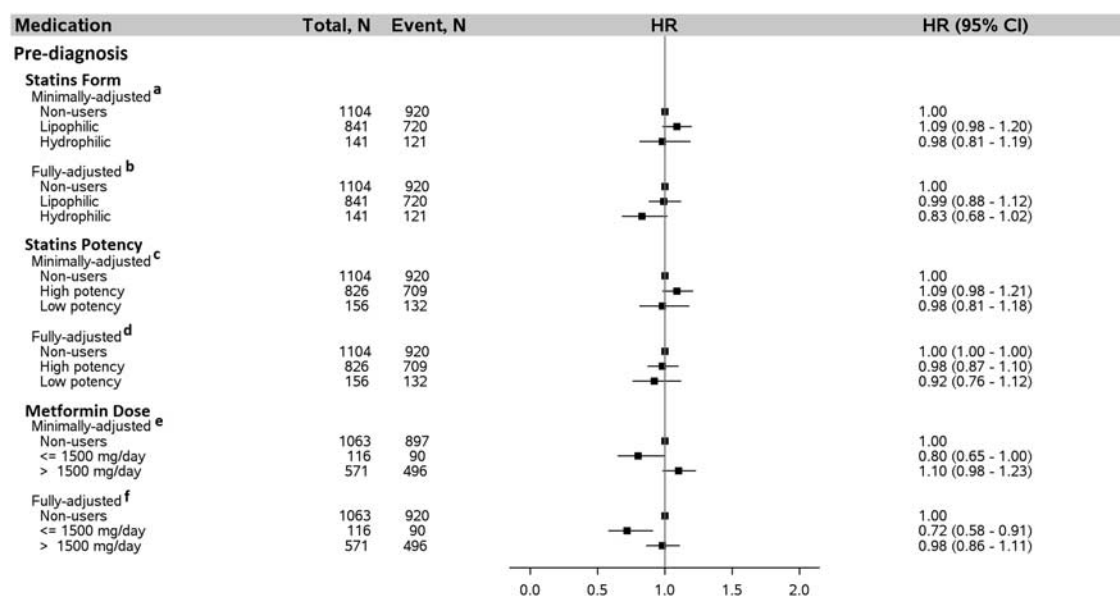
FIGURE 3. Kaplan-Meier survival curve for overall survival by prediagnosis medication use.
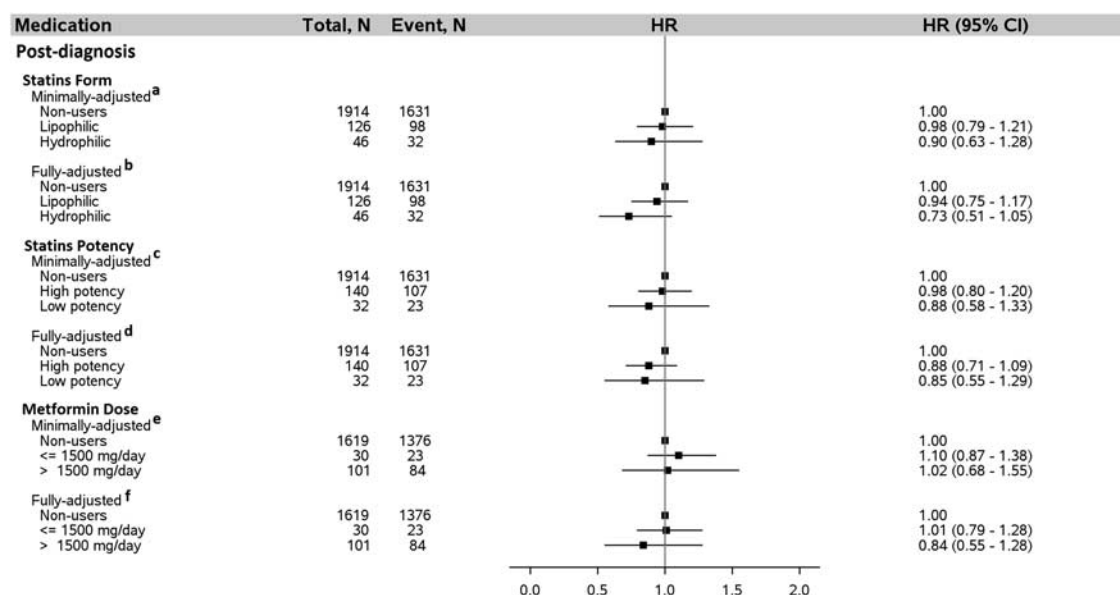
cirhosis. However, the association between metformin use and survival after diagnosis of HCC in individuals with T2DM is not clear. Some,[26,27] but not all,[28] studies have reported an inverse association between metformin use and mortality after HCC diagnosis. None of the existing studies examined independent

associations of prediagnosis or postdiagnosis metformin use while accounting for the effect of the other. In the present study, we found that average daily metformin dose ≤1500 mg/d taken before HCC diagnosis is associated with a 28% lower risk of death after diagnosis of HCC, adjusting for postdiagnosis metformin use, comorbidities, diabetes severity, tumor characteristics, and other relevant factors. However, prediagnosis metformin use in excess of 1500 mg/d and postdiagnosis metformin use were not associated with mortality after HCC diagnosis. From the perspective of cancer survival, metformin is known to inhibit cancer proliferation through induction of cell-cycle arrest and apoptosis,[45] promote of AMP-activated protein kinase signaling that result in inhibition of mammalian target of rapamycin (mTOR) pathway,[21,22] and attenuate metabolic abnormalities,[20] all of which could be mechanisms by which metformin may improve survival in HCC patients.

Many elderly patients with diabetes in the United States take both metformin and statins for management of T2DM and hyperlipidemia.[13,14] Statins, the HMG-CoA reductase inhibitors used primarily for hyperlipidemia, are thought to play a potential role in survival after HCC diagnosis.[24] Experimental studies suggest that statins inhibit HCC progression by promoting G1/S cell cycle arrest and enhancing apoptosis.[17] Other suggested mechanisms include inhibition of the P13K-AKT-mTOR pathway, which is

Medication	Total, N	Event, N	HR	HR (95% CI)
Pre-diagnosis				
Statins Form				
Minimally-adjusted [a]				
Non-users	1104	920		1.00
Lipophilic	841	720		1.09 (0.98 - 1.20)
Hydrophilic	141	121		0.98 (0.81 - 1.19)
Fully-adjusted [b]				
Non-users	1104	920		1.00
Lipophilic	841	720		0.99 (0.88 - 1.12)
Hydrophilic	141	121		0.83 (0.68 - 1.02)
Statins Potency				
Minimally-adjusted [c]				
Non-users	1104	920		1.00
High potency	826	709		1.09 (0.98 - 1.21)
Low potency	156	132		0.98 (0.81 - 1.18)
Fully-adjusted [d]				
Non-users	1104	920		1.00 (1.00 - 1.00)
High potency	826	709		0.98 (0.87 - 1.10)
Low potency	156	132		0.92 (0.76 - 1.12)
Metformin Dose				
Minimally-adjusted [e]				
Non-users	1063	897		1.00
<= 1500 mg/day	116	90		0.80 (0.65 - 1.00)
> 1500 mg/day	571	496		1.10 (0.98 - 1.23)
Fully-adjusted [f]				
Non-users	1063	920		1.00
<= 1500 mg/day	116	90		0.72 (0.58 - 0.91)
> 1500 mg/day	571	496		0.98 (0.86 - 1.11)

FIGURE 4. Association between statins form, statins potency, and metformin dose taken by patients with diabetes prediagnosis of HCC and risk of death after HCC diagnosis, N = 2499. [a]Adjusted for age (continuous), sex, and postdiagnosis statins form (lipophilic, hydrophilic, neither). Metformin only users were excluded from this analysis. [b]Adjusted for everything in "a" plus year of diagnosis, race, marital status, neighborhood income level, percent with 4-year college in neighborhood, tumor grade, tumor stage, chemotherapy, radiation, Charlson comorbidity index, diabetes severity index, obesity, COPD, dyslipidemia, and hepatitis status as categorized in Table 1. Metformin only users were excluded from the analysis. [c]Adjusted for age, sex, and postdiagnosis statins potency (high potency, low potency, nonusers). Metformin only users were not included in the analysis. [d]Adjusted for everything in "c" plus year of diagnosis, race, marital status, neighborhood income level, percent with 4-year college in neighborhood, tumor grade, tumor stage, chemotherapy, radiation, Charlson comorbidity index, diabetes severity index, obesity, COPD, dyslipidemia, and hepatitis as categorized in Table 1. Metformin only users were excluded from the analysis. [e]Adjusted for age (continuous), sex, and postdiagnosis metformin use dose (≤1500 mg/d, >1500 mg/d, nonusers). Statins only users were excluded from this analysis. [f]Adjusted for everything in "e" plus year of diagnosis, race, marital status, neighborhood income level, percent with 4-year college in neighborhood, tumor grade, tumor stage, chemotherapy, radiation, Charlson comorbidity index, diabetes severity index, obesity, COPD, dyslipidemia, and hepatitis as categorized in Table 1. Statins only users were excluded from the analysis. Abbreviation: HCC, hepatocellular carcinoma; COPD, chronic obstructive pulmonary disease. Lipophilic statins: atorvastatin, fluvastatin, lovastatin, and simvastatin. Hydrophilic statins: pravastatin and rosuvastatin. High potency statins: atorvastatin, rosuvastatin, and simvastatin. Low potency statins: fluvastatin, lovastatin, and pravastatin. COPD indicates chronic obstructive pulmonary disease; HCC, hepatocellular carcinoma.

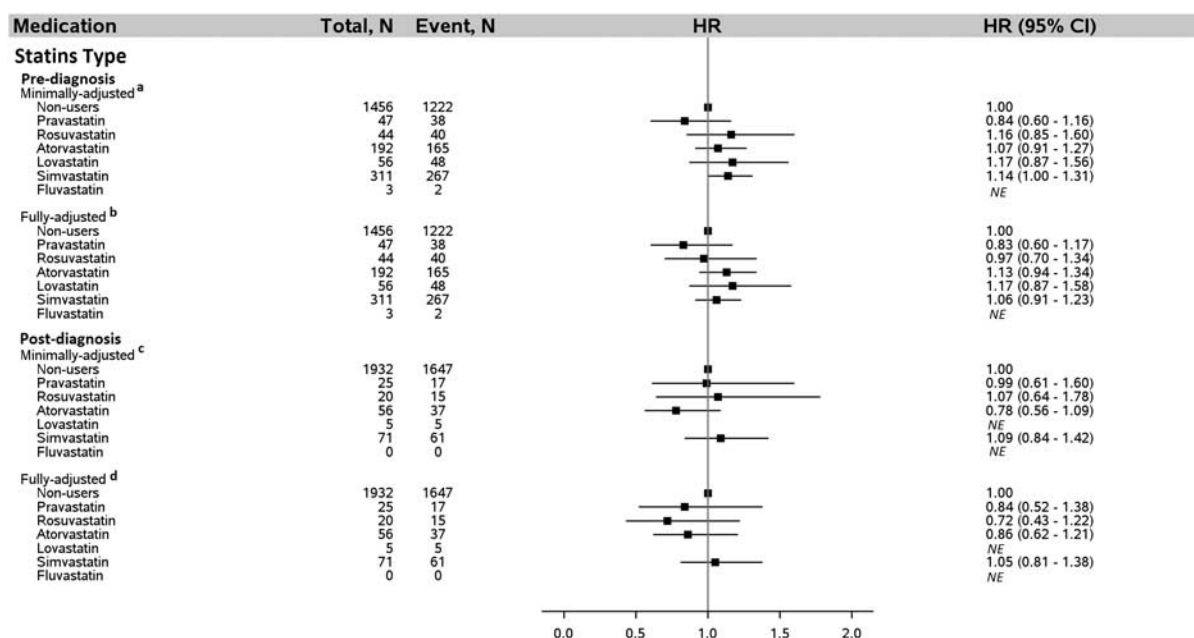| Medication	Total, N	Event, N	HR	HR (95% CI)
Post-diagnosis				
Statins Form				
Minimally-adjusted[a]				
Non-users	1914	1631		1.00
Lipophilic	126	98		0.98 (0.79 - 1.21)
Hydrophilic	46	32		0.90 (0.63 - 1.28)
Fully-adjusted[b]				
Non-users	1914	1631		1.00
Lipophilic	126	98		0.94 (0.75 - 1.17)
Hydrophilic	46	32		0.73 (0.51 - 1.05)
Statins Potency				
Minimally-adjusted[c]				
Non-users	1914	1631		1.00
High potency	140	107		0.98 (0.80 - 1.20)
Low potency	32	23		0.88 (0.58 - 1.33)
Fully-adjusted[d]				
Non-users	1914	1631		1.00
High potency	140	107		0.88 (0.71 - 1.09)
Low potency	32	23		0.85 (0.55 - 1.29)
Metformin Dose				
Minimally-adjusted[e]				
Non-users	1619	1376		1.00
<= 1500 mg/day	30	23		1.10 (0.87 - 1.38)
> 1500 mg/day	101	84		1.02 (0.68 - 1.55)
Fully-adjusted[f]				
Non-users	1619	1376		1.00
<= 1500 mg/day	30	23		1.01 (0.79 - 1.28)
> 1500 mg/day	101	84		0.84 (0.55 - 1.28)

HR axis: 0.0   0.5   1.0   1.5   2.0

FIGURE 5. Association between statins form, statins potency, and metformin dose taken by patients with diabetes postdiagnosis of HCC and risk of death after HCC diagnosis, N = 2499. [a]Adjusted for age (continuous), sex, and prediagnosis statins form (lipophilic, hydrophilic, neither). Metformin only users were excluded from this analysis. [b]Adjusted for everything in "a" plus year of diagnosis, race, marital status, neighborhood income level, percent with 4-year college in neighborhood, tumor grade, tumor stage, chemotherapy, radiation, Charlson comorbidity index, diabetes severity index, obesity, COPD, dyslipidemia, and hepatitis status as categorized in Table 1. Metformin only users were excluded from the analysis. [c]Adjusted for age, sex, and prediagnosis statins potency (high potency, low potency, nonusers). Metformin only users were not included in the analysis. [d]Adjusted for everything in "c" plus year of diagnosis, race, marital status, neighborhood income level, percent with 4-year college in neighborhood, tumor grade, tumor stage, chemotherapy, radiation, Charlson comorbidity index, diabetes severity index, obesity, COPD, dyslipidemia, and hepatitis as categorized in Table 1. Metformin only users were excluded from the analysis. [e]Adjusted for age (continuous), sex, and prediagnosis metformin use dose (≤1500 mg/d, >1500 mg/d, nonusers). Statins only users were excluded from this analysis. [f]Adjusted for everything in "e" plus year of diagnosis, race, marital status, neighborhood income level, percent with 4-year college in neighborhood, tumor grade, tumor stage, chemotherapy, radiation, Charlson comorbidity index, diabetes severity index, obesity, COPD, dyslipidemia, and hepatitis as categorized in Table 1. Statins only users were excluded from the analysis. Lipophilic statins: atorvastatin, fluvastatin, lovastatin, and simvastatin. Hydrophilic statins: pravastatin and rosuvastatin. High potency statins: atorvastatin, rosuvastatin, and simvastatin. Low potency statins: fluvastatin, lovastatin, and pravastatin. COPD indicates chronic obstructive pulmonary disease; HCC, hepatocellular carcinoma.

important for cancer cell survival.[18] It is worth noting that not all statins have hepatic-selectivity or enhanced suppression of HMG-CoA reductase. Lipophilic statins (ie, atorvastatin, fluvastatin, lovastatin, and simvastatin) permeate both hepatic and extrahepatic cells with passive diffusion, while hydrophilic statins (ie, pravastatin and rosuvastatin) selectively accumulate in the liver through a reaction mediated by transporters expressed in hepatocytes.[24,35] The discriminatory accumulation of hydrophilic statins in the liver suggests that they may have some role in liver cancer risk and progression.[24] In this context, pravastatin has been found to impede the progression and metastasis of established HCC.[15] Few epidemiologic studies have examined the association between statins use and mortality after HCC diagnosis.[24,25] Jeon et al[24] did not find an association between use of pravastatin and overall survival after diagnosis of stage I or II HCC in an observational study, while in a clinical trial, Kawata et al[25] found that pravastatin use prolonged survival of patients with advance HCC. In the present study, overall statins use (hydrophilic and lipophilic combined) either prediagnosis or postdiagnosis was not associated with survival after HCC diagnosis, neither was combined use of statins and metformin. No association was also found when statins were grouped into their functional forms (lipophilic vs. hydrophilic) or when individual statins were examined. Given the generally limited data on statins use and survival of HCC patients coupled with the

inconclusive findings among existing studies, further studies, including from randomized controlled trials, are needed before firm conclusions can be drawn about the role of statins in overall survival of diabetic HCC patients.

Our study has several strengths and limitations. It is limited by the use of SEER-Medicare data that restricted the study population to elderly patients of age 65 years or older. Hence, the findings may not be applicable to younger patients. Information on medication use before age 65 years are not available in the SEER-Medicare data; this could have led to misclassification of medication use and may have biased the results to some extent. Moreover, the retrospective nature of the data precludes causal inferences about metformin exposure and mortality after HCC diagnosis. Because the Medicare claims data are designed for billing purposes, detail information on some of the study variables, such as radiation dose, chemotherapy type and dose, were not available. Thus, there is the possibility of residual confounding by these factors. Confounding by unmeasured factors, such as tobacco smoking history, extent of liver injury, and blood cholesterol levels also cannot be ruled out. Severity of liver injury is often measured by circulating levels of aspartate aminotransferase (AST) and aminotransferase (ALT). Statins use is contra-indicated in patients with extremely high ALT;[46] hence, patients with high ALT levels, for example, may not have

Medication	Total, N	Event, N	HR	HR (95% CI)
Statins Type				
Pre-diagnosis				
Minimally-adjusted [a]				
Non-users	1456	1222		1.00
Pravastatin	47	38		0.84 (0.60 - 1.16)
Rosuvastatin	44	40		1.16 (0.85 - 1.60)
Atorvastatin	192	165		1.07 (0.91 - 1.27)
Lovastatin	56	48		1.17 (0.87 - 1.56)
Simvastatin	311	267		1.14 (1.00 - 1.31)
Fluvastatin	3	2		NE
Fully-adjusted [b]				
Non-users	1456	1222		1.00
Pravastatin	47	38		0.83 (0.60 - 1.17)
Rosuvastatin	44	40		0.97 (0.70 - 1.34)
Atorvastatin	192	165		1.13 (0.94 - 1.34)
Lovastatin	56	48		1.17 (0.87 - 1.58)
Simvastatin	311	267		1.06 (0.91 - 1.23)
Fluvastatin	3	2		NE
Post-diagnosis				
Minimally-adjusted [c]				
Non-users	1932	1647		1.00
Pravastatin	25	17		0.99 (0.61 - 1.60)
Rosuvastatin	20	15		1.07 (0.64 - 1.78)
Atorvastatin	56	37		0.78 (0.56 - 1.09)
Lovastatin	5	5		NE
Simvastatin	71	61		1.09 (0.84 - 1.42)
Fluvastatin	0	0		NE
Fully-adjusted [d]				
Non-users	1932	1647		1.00
Pravastatin	25	17		0.84 (0.52 - 1.38)
Rosuvastatin	20	15		0.72 (0.43 - 1.22)
Atorvastatin	56	37		0.86 (0.62 - 1.21)
Lovastatin	5	5		NE
Simvastatin	71	61		1.05 (0.81 - 1.38)
Fluvastatin	0	0		NE

(HR axis: 0.0 0.5 1.0 1.5 2.0)

FIGURE 6. Association between individual statins type used by diabetics both prediagnosis and postdiagnosis of HCC and risk of death after diagnosis of HCC. [a]Adjusted for age (continuous), sex, and postdiagnosis statins type (pravastatin, rosuvastatin, atorvastatin, lovastatin, simvastatin, fluvastatin, and nonusers). [b]Adjusted for everything in "a" plus year of diagnosis, race, marital status, neighborhood income level, percent with 4-year college in neighborhood, tumor grade, tumor stage, chemotherapy, radiation, Charlson comorbidity index, diabetes severity index, obesity, presence of COPD, dyslipidemia, and hepatitis as categorized in Table 1. [c]Adjusted for age, sex, and prediagnosis statins type (pravastatin, rosuvastatin, atorvastatin, lovastatin, simvastatin, fluvastatin, and nonusers). [d]Adjusted for everything in "c" plus year of diagnosis, race, marital status, neighborhood income level, percent with 4-year college in neighborhood, tumor grade, tumor stage, chemotherapy, radiation, Charlson comorbidity index, obesity, COPD, dyslipidemia, diabetes, diabetic comorbidities index, and hepatitis status as categorized in Table 1. COPD indicates chronic obstructive pulmonary disease; HCC, hepatocellular carcinoma; NE, not estimated because of small numbers (< 10 individuals in the group).

been prescribed statins. The absence of information on circulating ALT and AST levels could have confounded the findings either toward or away from null. Additionally, low blood cholesterol level would lead to less frequent use of statins, which we were unable to assess or account for in the analysis. Despite these limitations, the data source provided comprehensive, population-based resource for investigating the impact of medication use on cancer outcomes and included detail patient information, such as comorbidities and indices of diabetes severity, which were accounted for in the analyses. Additional strengths include the ability to control for postdiagnosis medication use when examining association for prediagnosis use and vice versa. The large sample size and stringent HCC case definition, which excluded potential metastatic cases, add to the study strengths.

The findings of this study suggest that prediagnosis use of metformin dose ≤ 1500 mg/d may improve overall survival of elderly diabetic HCC patients. Given the sparse data on associations between prediagnosis metformin dose and overall survival after HCC diagnosis, verifications are warranted in larger prospective studies with adequate representation of younger patients.

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