Received: 30 March 2021 | Revised: 1 July 2021 | Accepted: 22 July 2021

DOI: 10.1002/hsr2.352

RESEARCH ARTICLE

Health Science Reports Open Access WILEY

# Association of metformin use on metabolic acidosis in diabetic patients with chronic hepatitis B-related cirrhosis and renal impairment

Terry Cheuk-Fung Yip[1,2,3] | Raymond Ngai Chiu Chan[1] | Vincent Wai-Sun Wong[1,2,3] | Yee-Kit Tse[1,2,3] | Lilian Yan Liang[1] | Vicki Wing-Ki Hui[1] | Xinrong Zhang[1] | Guan-Lin Li[1] | Henry Lik-Yuen Chan[2,4,5] | Grace Lai-Hung Wong[1,2,3]

[1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China

[2]Medical Data Analytics Centre (MDAC), The Chinese University of Hong Kong, Hong Kong, China

[3]Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, China

[4]Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

[5]Department of Internal Medicine, Union Hospital, Hong Kong

**Correspondence**
Grace Lai-Hung Wong, Department of Medicine and Therapeutics, 9/F Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, Hong Kong.
Email: wonglaihung@cuhk.edu.hk

## Abstract

**Background and Aims:** Metformin is an oral anti-hyperglycemic recommended by the American Diabetes Association (ADA) as a preferred initial pharmacologic agent for type 2 diabetes. Metabolic acidosis is a rare yet severe side effect of it. We examined the association of metformin use and dosage on the risk of metabolic acidosis in diabetic patients with different degrees of chronic hepatitis B (CHB)-related cirrhosis and chronic kidney disease (CKD).

**Methods:** Metabolic acidosis was defined by blood pH ≤7.35, together with lactate >5 mmol/L or arterial bicarbonate ≤18 mmol/L or venous bicarbonate ≤21 mmol/L, and/or diagnosis codes. Child-Pugh class and CKD stage were included in the model as time-dependent covariates. Age, gender, comorbidities, and use of relevant medications were adjusted as covariates. Maximum daily dose of metformin was classified into ≤1000 mg and >1000 mg.

**Results:** We identified 4431 diabetic patients with CHB-related cirrhosis between 2000 and 2017 from a territory-wide database in Hong Kong. The risk of metabolic acidosis increased with Child-Pugh class B and C cirrhosis regardless of CKD stage (adjusted subdistribution hazard ratio [aSHR] ranged from 3.50 to 86.16). Metformin use was associated with a higher risk in patients with Child-Pugh class B or C cirrhosis and stage 3A CKD or above (aSHR ranged from 1.55 to 2.46). In stage 4/5 CKD, a daily dose of metformin ≤1000 mg was still associated with a higher risk of metabolic acidosis regardless of the severity of cirrhosis (aSHR ranged from 2.45 to 3.92).

**Conclusion:** In conclusion, patients with Child-Pugh class B cirrhosis or above were at a higher risk of metabolic acidosis. Metformin further increased the risk in patients

**Abbreviations:** ADA, American Diabetes Association; CDARS, Clinical Data Analysis and Reporting System; CHB, chronic hepatitis B; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IHD, ischemic heart disease; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy.

Terry Yip and Raymond Chan have contributed equally to this work.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2021 The Authors. *Health Science Reports* published by Wiley Periodicals LLC.

with Child-Pugh class B cirrhosis or above and stage 3A CKD or above. Dose adjustment in stage 4/5 CKD did not reduce the risk of metabolic acidosis.

**KEYWORDS**
Child-Pugh score, chronic kidney diseases, hepatic complications, metabolic acidosis, metformin

## 1 | INTRODUCTION

Diabetes mellitus (DM) is a rising global health problem characterized by insulin resistance and/ or insufficiency. Current estimation indicates a total of 463 million DM patients worldwide and predicts a further rise of 51% by 2045.[1] Metformin, an oral antihyperglycemic agent under the class biguanide, is recommended by the American Diabetes Association (ADA) as a preferred initial pharmacologic agent for type 2 diabetic patients.[2] It is associated with low hypoglycemic risk when used as monotherapy, reduced the risk of hepatocellular carcinoma (HCC), and all-cause mortality.[2-4] While it is generally safe, metabolic acidosis has been recognized as a rare, yet serious adverse event. This is possibly due to the inhibition of mitochondrial respiration in the liver and muscles, which are responsible for lactate removal.[5-7] Among patients with kidney injury, *that is*, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 $m^2$, previous studies showed that metformin use was associated with an elevated risk of acidosis.[8]

Up to now, whether metformin can be safely used in patients with liver cirrhosis remains questionable. While metformin should be cautiously used in case of decompensated cirrhosis due to concerns of increased risk of metabolic acidosis with possibly impaired hepatic lactate clearance,[9] a retrospective study showed that metformin use in diabetic patients significantly improved survival even after the diagnosis of cirrhosis.[10] In diabetic patients with non-alcoholic steatohepatitis-related cirrhosis, metformin use was found to be associated with better clinical outcomes including lower rates of HCC incidence and mortality.[11,12] Other studies also reported that metformin use was associated with reduced HCC incidence in diabetic patients, with or without coexisting chronic liver diseases.[13-16] Currently, the Food and Drug Administration official "label" advise against the use of metformin in patients with hepatic impairment.

While metformin related metabolic acidosis is generally a rare adverse event with an estimated incidence of around 0.03 per 1000 patient year,[17] data from large-scale population-based studies looking into metformin related metabolic acidosis in cirrhotic patients remain scarce. Hence, we aimed to examine the association between metformin use and risk of metabolic acidosis in patients with DM and chronic hepatitis B (CHB)-related cirrhosis under different severity of chronic kidney disease (CKD). We also evaluated the association between the daily dose of metformin and risk of metabolic acidosis.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and data source

We performed a territory-wide retrospective cohort study using data from the Clinical Data Analysis and Reporting System (CDARS) of the Hospital Authority, Hong Kong. CDARS facilitates the retrieval of clinical data captured from different operational systems for analysis and reporting, providing good quality information to support retrospective clinical and management decisions by integrating the clinical data resided in Data Warehouse.[18] The Hospital Authority is the sole public healthcare provider in Hong Kong. CDARS captures in-patient and out-patient clinical data from all public hospitals and clinics in Hong Kong to represents data of approximately 80% of the local population.[19] All data are anonymized in CDARS to ensure confidentiality. Multiple studies were conducted previously using data from CDARS.[20-22] The study protocol was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee. Informed consent was exempted due to the anonymized nature of the data.

### 2.2 | Subjects

All DM patients with positive hepatitis B surface antigen (HBsAg) and liver cirrhosis from January 1, 2000 to December 31, 2017 in Hong Kong were identified. DM was defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for DM (250—diabetes mellitus), and/or exposure to any anti-diabetic agents, and/or hemoglobin $A_{1c}$ ($HbA_{1c}$) ≥6.5%, and/or fasting plasma glucose ≥7 mmol/L in two measurements or ≥11.1 mmol/L in one measurement.[23] Patients younger than 18 years old at DM diagnosis, those with metabolic acidosis prior to baseline, acute hepatitis B, hepatitis C, hepatitis D virus or human immunodeficiency virus (HIV) coinfection, other autoimmune or metabolic liver diseases, eGFR <30 mL/min/1.73 $m^2$ or on renal replacement therapy at DM diagnosis, as well as those without cirrhosis or with missing Child-Pugh score at baseline and/or during follow-up were excluded. Metformin users were defined by exposure to metformin at baseline or during follow-up. Patients were followed from baseline until the date of metabolic acidosis, death, last follow-up date (December 31, 2017), or up to 16 years of follow-up, whichever came first.

### 2.3 | Data collection

Data were retrieved from the CDARS in January 2018. Baseline date was defined as the date of first diagnosis of DM in the database consisting of data from January 1, 2000 to December 31, 2017. Demographic data including gender, date of birth, and date of registered death were captured. At baseline, liver and renal biochemistries, hematological, and virological parameters were collected. Thereafter, serial liver and renal biochemistries as well as hepatitis B virus (HBV) viral markers (HBsAg, hepatitis B e antigen [HBeAg], HBV DNA) were collected until the last follow-up date (Table S1). We also retrieved data on other relevant diagnoses, procedures, concomitant drugs, laboratory parameters, and exposure to nucleos(t)ide analogs (ie, adefovir dipivoxil, entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide, lamivudine, and telbivudine), and (pegylated)-interferon for any duration (Tables S2 and S3).

### 2.4 | Definitions

The primary endpoint was metabolic acidosis. Metabolic acidosis was defined by blood pH ≤7.35 with lactate >5 mmol/L or arterial bicarbonate ≤18 mmol/L or venous bicarbonate ≤21 mmol/L, and/or diagnosis codes. Liver cirrhosis was identified by ICD-9-CM diagnosis codes for cirrhosis and its related complications (Table S3). Hypertension was identified by ICD-9-CM diagnosis codes and/or any use of anti-hypertensive drugs. Acute hepatitis B, hepatitis C, hepatitis D virus or HIV coinfection, HCC, ischemic heart disease (IHD), cerebrovascular events (CVA), congestive heart failure (CHF), and renal replacement therapy (RRT) were identified by their respective diagnosis codes (Table S3). Stage 1, 2, 3A, 3B, and 4 or above CKD were defined as estimated glomerular filtration rate >90, 89 to 60, 59 to 45, 44 to 30, and <30 mL/min/1.73 $m^2$, respectively. Maximum daily dose of metformin was categorized into ≤1000 and >1000 mg. The use of a single ICD-9-CM code for diagnosis have been found 99% accurate when referenced to clinical, laboratory, imaging, and endoscopy results from the electronic medical records.[24]

### 2.5 | Statistical analysis

Data were analyzed using Statistical Product and Service Solutions (SPSS) version 25.0 (SPSS, Inc., Chicago, Illinois), SAS (9.4; SAS Institute Inc., Cary, NC), and R software (4.0.2; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed in mean ± SD or median (interquartile range [IQR]), as appropriate, while categorical variables were presented as frequency (percentage). Qualitative and quantitative differences between groups were analyzed by chi-square or Fisher's exact tests for categorical parameters and Student's *t* test, Mann-Whitney test, one-way ANOVA, and Kruskal-Wallis test for continuous parameters, as appropriate. Cumulative incidence function of metabolic acidosis with adjustment of competing death was estimated with a 95% confidence interval (CI) by Gray's method. Subdistribution hazard ratios and adjusted subdistribution hazard ratios (aSHR) with 95% CI were estimated with Fine-Gray proportional subdistribution hazards regression with adjustment of competing death.[25] We included the use of DM medications including metformin, sulphonylureas, alpha glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, thiazolidinedione, and insulin, as well as the use of other medication including diuretics, statins, aspirin/clopidogrel, nonsteroidal anti-inflammatory drug, angiotensin-converting-enzyme inhibitors/ angiotensin II receptor blockers, beta blockers, and calcium channel blockers in the univariate and multivariable analyses. The use of medications was included as time-dependent covariates according to treatment initiation or discontinuation. Child-Pugh class and eGFR category were also included as time-dependent covariates. We included the main effect of Child-Pugh class and eGFR category, the two-way interaction of Child-Pugh class and eGFR category, and their individual two-way interaction with metformin use. We also included the following covariates: age, gender, presence of hypertension, IHD, CHF, CVA, and RRT during follow-up; important covariates were selected by backward selection. In the analysis of the association between the dose of metformin and the risk of metabolic acidosis, we included the time-dependent maximum daily dose of metformin in the multivariable model, with the adjustment of time-dependent Child-Pugh class and eGFR category. All statistical tests were two-sided. Statistical significance was taken as $P < .05$.

## 3 | RESULTS

### 3.1 | Baseline characteristics

A total of 35 837 potentially eligible patients with positive HBsAg and DM were identified from January 1, 2000 to December 31, 2017, of which 31 406 were excluded: 16 younger than 18 years old at baseline; 716 with acute hepatitis B; 401, 8, and 66 with HCV, HDV, and HIV coinfection, respectively; 220 with metabolic acidosis before baseline; 390 with eGFR <30 mL/min/1.73 $m^2$ or on RRT, 25 with other autoimmune or metabolic liver diseases, as well as 29 512 and 52 without cirrhosis or Child-Pugh score, respectively (Figure 1). As a result, 4431 patients were included in the final analysis. Their mean age was 60.8 ± 10.8 years and 3216 (72.6%) were male. Most patients were in stage 1 (35.9%) or 2 (45.8%) CKD and Child-Pugh class A cirrhosis (72.6%; Table 1).

Of 4431 patients, 2670 (60.3%) were metformin users; 1132 (42.4%) were on metformin at baseline and 1538 (57.6%) were started on metformin during follow-up. Compared to non-users, metformin users were younger, and had less advanced cirrhosis and fewer comorbidities including IHD, CHF, CVA, and HT at baseline. More of them were on thiazide diuretic, but fewer were on potassium-sparing or loop diuretics. Clinical characteristics of metformin users and non-metformin users are summarized in Table 2.

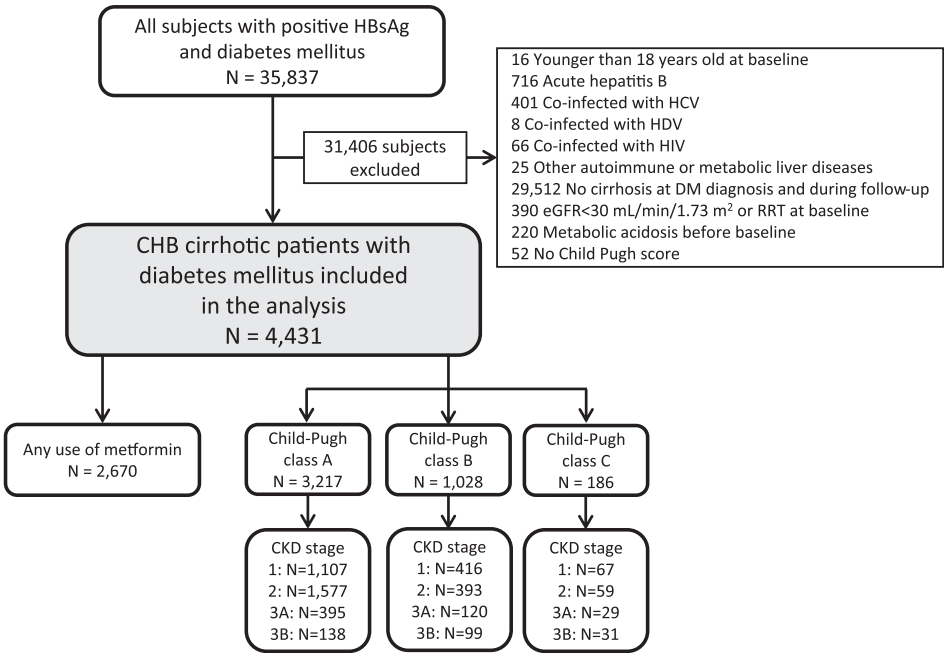


**FIGURE 1** Patient flow chart. CHB, chronic hepatitis B; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; RRT, renal replacement therapy

### 3.2 | Association of CKD stage and Child-Pugh class on metabolic acidosis

At a median follow-up of 5.3 (2.0-9.7) years, a total of 1060 (23.9%) patients developed metabolic acidosis, of which 626 (23.4%) were metformin users. At baseline, 1590 (35.9%), 2029 (45.8%), 544 (12.3%), and 268 (6.0%) patients were in stage 1, 2, 3A, and 3B CKD, respectively Among patients with Child-Pugh class A, B, and C at baseline, the proportion of patients with CKD stage 3A-B were 16.6%, 21.3%, and 32.3%, respectively (Table 1). During follow-up, 271 (6.1%), 1158 (26.1%), 685 (15.5%), 807 (18.2%), 898 (20.3%), and 612 (13.8%) patients developed the highest CKD stage of 1, 2, 3A, 3B, 4, and 5, respectively. A multivariable model adjusted for baseline age, gender, CHF, RRT in follow-up, use of insulin, use of diuretics, and use of nonsteroidal anti-inflammatory drugs (NSAIDs) showed that patients with Child-Pugh class B cirrhosis, regardless of their eGFR, were associated with an increased risk of metabolic acidosis when compared to patients with stage 1 CKD and Child-Pugh class A cirrhosis. The corresponding aSHR were 3.50 (95% CI: 2.28-5.36, $P < .001$), 3.88 (95% CI: 2.52-5.99, $P < .001$), 9.51 (95% CI: 6.11-14.82, $P < .001$), 15.88 (95% CI: 10.28-24.53, $P < .001$) and 61.33 (95% CI: 40.98-91.79, $P < .001$) in patients with stage 1, 2, 3A, 3B, and 4/5 CKD, respectively. Those with Child-Pugh class C cirrhosis were associated with even higher risks when compared to those with class B and corresponding CKD stage. Similarly, patients in stage 3B CKD or above, irrespective to the Child-Pugh classes, were associated with a higher risk of metabolic acidosis (Table 3).

### 3.3 | Association of metformin on metabolic acidosis in different CKD stage and Child-Pugh class

We constructed another multivariable model to evaluate the additional associations of metformin on metabolic acidosis in different CKD stages and Child-Pugh classes. The aSHR for metformin users in stage 4 CKD or above were 1.97 (95% CI: 1.31-2.97, $P = .001$), 2.46 (95% CI: 1.67-3.63, $P < .001$) and 2.41 (95% CI: 1.47-3.96, $P < .001$) amongst those with Child-Pugh class A, B, and C cirrhosis, respectively, as compared to non-metformin users in the same Child-Pugh class and CKD stage. The association between metformin use in patients with Child-Pugh class B or above were also significant amongst those with stage 3A CKD or above, except in those with stage 3A or 3B CKD and Child-Pugh class C cirrhosis (Table 4).

### 3.4 | Association of daily metformin dose on metabolic acidosis

In patients with stage 4 CKD or above, a maximum daily metformin dose of >1000 mg was significantly correlated with metabolic acidosis regardless of their Child-Pugh classes when compared to non-metformin users with the same CKD stage and Child-Pugh class. The aSHR in those patients were 1.87 (95% CI: 1.15-3.02, $P = .011$), 2.20 (95% CI: 1.39-3.49; $P = .001$) and 1.93 (95% CI: 1.05-3.53, $P = .033$) for those with Child-Pugh class A, B, and C cirrhosis, respectively. Meanwhile, a lower risk of metabolic acidosis was not observed in a lower daily metformin dose in subgroups of CKD stage and Child-Pugh class. The aSHR for patients on ≤1000 mg metformin were 2.45 (95% CI: 1.25-4.78, $P = .009$), 3.30 (95% CI: 1.73-6.29; $P < .001$) and 3.92 (95% CI: 1.73-8.86; $P = .001$) amongst those with stage 4 CKD or above and Child-Pugh class A, B, or C cirrhosis, respectively (Table 5).

## 4 | DISCUSSION

We performed a territory-wide retrospective cohort study to evaluate the risk of metabolic acidosis associated with use of metformin in DM

**TABLE 1** Baseline clinical characteristics of patients with Child-Pugh class A, B, and C at baseline

| Clinical characteristics | All patients N = 4431 | Child-Pugh class A N = 3217 | Child-Pugh class B N = 1028 | Child-Pugh class C N = 186 | *P* value |
|---|---|---|---|---|---|
| Age (years) | 60.8 ± 10.8 | 60.7 ± 10.6 | 61.3 ± 11.1 | 59.2 ± 11.1 | 0.028 |
| Male gender (n, %) | 3216 (72.6) | 2310 (71.8) | 763 (74.2) | 143 (76.9) | 0.129 |
| eGFR (ml/min/1.73m$^2$) (n, %) | | | | | <0.001 |
| ≥90 | 1590 (35.9) | 1107 (34.4) | 416 (40.5) | 67 (36.0) | |
| 60-89 | 2029 (45.8) | 1577 (49.0) | 393 (38.2) | 59 (31.7) | |
| 45-59 | 544 (12.3) | 395 (12.3) | 120 (11.7) | 29 (15.6) | |
| 30-44 | 268 (6.0) | 138 (4.3) | 99 (9.6) | 31 (16.7) | |
| $HbA_{1c}$ (%) | 7.9 ± 2.3 | 8.0 ± 2.2 | 7.8 ± 2.6 | 7.0 ± 2.5 | 0.001 |
| Missing (%) | 18.1 | 12.8 | 28.7 | 51.1 | |
| Alanine aminotransferase (U/L) | 42 (27-70) | 40 (26-64) | 47 (29-82) | 57 (34-112) | <0.001 |
| Missing (%) | 1.1 | 1.1 | 0.9 | 2.2 | |
| Positive HBeAg (n, %)[a] | 632 (20.2) | 450 (19.3) | 147 (21.8) | 35 (25.9) | 0.086 |
| Missing (%) | 29.2 | 27.7 | 34.4 | 27.4 | |
| HBV DNA (log IU/mL) | 3.9 ± 2.6 | 3.9 ± 2.6 | 4.0 ± 2.6 | 3.2 ± 2.6 | 0.134 |
| Missing (%) | 62.7 | 60.2 | 69.5 | 69.9 | |
| *Comorbidities (n, %)* | | | | | |
| Ischemic heart disease | 147 (3.3) | 113 (3.5) | 30 (2.9) | 4 (2.2) | 0.431 |
| Congestive heart failure | 94 (2.1) | 56 (1.7) | 30 (2.9) | 8 (4.3) | 0.008 |
| Cerebrovascular accident | 146 (3.3) | 100 (3.1) | 38 (3.7) | 8 (4.3) | 0.481 |
| Hypertension | 2628 (59.3) | 1857 (57.7) | 632 (61.5) | 139 (74.7) | <0.001 |
| *NA therapy (n, %)* | 3104 (70.1) | 2314 (71.9) | 654 (63.6) | 136 (73.1) | <0.001 |
| Entecavir | 2432 (54.9) | 1848 (57.4) | 481 (46.8) | 103 (55.4) | <0.001 |
| Tenofovir disoproxil fumarate | 392 (8.8) | 294 (9.1) | 80 (7.8) | 18 (9.7) | 0.378 |
| Lamivudine | 993 (22.4) | 674 (21) | 262 (25.5) | 57 (30.6) | <0.001 |
| Telbivudine | 217 (4.9) | 168 (5.2) | 41 (4.0) | 8 (4.3) | 0.260 |
| Adefovir dipivoxil | 325 (7.3) | 239 (7.4) | 72 (7) | 14 (7.5) | 0.897 |
| *Medication use at baseline (n, %)* | | | | | |
| Metformin | 1132 (25.5) | 961 (29.9) | 161 (15.7) | 10 (5.4) | <0.001 |
| Sulfonylureas | 1745 (39.4) | 1321 (41.1) | 380 (37) | 44 (23.7) | <0.001 |
| DPP-4 inhibitor | 4 (0.1) | 4 (0.1) | 0 (0) | 0 (0) | 0.645 |
| Alpha glucosidase inhibitor | 51 (1.2) | 46 (1.4) | 4 (0.4) | 1 (0.5) | 0.018 |
| Insulin | 528 (11.9) | 238 (7.4) | 206 (20) | 84 (45.2) | <0.001 |
| Thiazolidinedione | 5 (0.1) | 4 (0.1) | 1 (0.1) | 0 (0) | 1.000 |
| Statin | 231 (5.2) | 195 (6.1) | 33 (3.2) | 3 (1.6) | <0.001 |
| ACEI or ARB | 777 (17.5) | 635 (19.7) | 135 (13.1) | 7 (3.8) | <0.001 |
| Beta blockers | 1389 (31.3) | 921 (28.6) | 370 (36) | 98 (52.7) | <0.001 |
| Calcium channel blockers | 992 (22.4) | 821 (25.5) | 155 (15.1) | 16 (8.6) | <0.001 |
| Thiazide diuretics | 271 (6.1) | 236 (7.3) | 34 (3.3) | 1 (0.5) | <0.001 |
| Potassium-sparing diuretics | 819 (18.5) | 313 (9.7) | 376 (36.6) | 130 (69.9) | <0.001 |
| Loop diuretics | 741 (16.7) | 282 (8.8) | 345 (33.6) | 114 (61.3) | <0.001 |
| Aspirin or clopidogrel | 410 (9.3) | 328 (10.2) | 76 (7.4) | 6 (3.2) | <0.001 |
| NSAID | 606 (13.7) | 507 (15.8) | 91 (8.9) | 8 (4.3) | <0.001 |
| Follow-up duration from baseline (years) | 5.3 (2.0–9.7) | 6.6 (3.3-10.8) | 2.2 (0.6-5.9) | 0.4 (0.02-2.0) | <0.001 |

*Note:* Alanine aminotransferase and follow-up duration were expressed in median (interquartile range), whereas other continuous variables were expressed in mean ± SD. All comorbidities medications were represented as binary parameters. Qualitative and quantitative differences between groups were analyzed by chi-square or Fisher's exact tests for categorical parameters and one-way ANOVA or Kruskal-Wallis test for continuous parameters, as appropriate.

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; $HbA_{1c}$, hemoglobin $A_{1c}$; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IQR, interquartile range; NA, nucleos(t)ide analogs' NSAID, nonsteroidal anti-inflammatory drug.

[a]Percentages were based on non-missing data.

**TABLE 2** Baseline clinical characteristics of metformin users and non-metformin users

| Clinical characteristics | Metformin user N = 2670 | Non-metformin users N = 1761 | *P* value |
|---|---|---|---|
| Age (years) | 59.9 ± 10.5 | 62.1 ± 11.0 | <0.001 |
| Male gender (n, %) | 1863 (69.8) | 1353 (76.8) | <0.001 |
| eGFR (ml/min/1.73m$^2$) (n, %) | | | <0.001 |
| ≥90 | 1027 (38.5) | 563 (32.0) | |
| 60-89 | 1270 (47.6) | 759 (43.1) | |
| 45-59 | 288 (10.8) | 256 (14.5) | |
| 30-44 | 85 (3.2) | 183 (10.4) | |
| Child-Pugh class (n, %) | | | <0.001 |
| A | 2232 (83.6) | 985 (55.9) | |
| B | 411 (15.4) | 617 (35.0) | |
| C | 27 (1.0) | 159 (9.0) | |
| $HbA_{1c}$ (%) | 8.2 ± 2.3 | 7.3 ± 2.2 | <0.001 |
| Missing (%) | 303 (11.3) | 500 (28.4) | |
| Alanine aminotransferase (U/L) | 43 (28-69) | 42 (27-71) | 0.367 |
| Missing (%) | 0.9 | 1.4 | |
| Positive HBeAg (n, %)[a] | 394 (20.2) | 238 (20.0) | 0.867 |
| Missing (%) | 27.1 | 32.4 | |
| HBV DNA (log IU/mL) | 4.3 ± 2.5 | 3.2 ± 2.7 | <0.001 |
| Missing (%) | 59.0 | 68.4 | |
| *Comorbidities (n, %)* | | | |
| Ischemic heart disease | 70 (2.6) | 77 (4.4) | 0.002 |
| Congestive heart failure | 33 (1.2) | 61 (3.5) | <0.001 |
| Cerebrovascular accident | 46 (1.7) | 100 (5.7) | <0.001 |
| Hypertension | 1427 (53.4) | 1201 (68.2) | <0.001 |
| *NA therapy (n, %)* | *1967 (73.7)* | *1137 (64.6)* | *<0.001* |
| Entecavir | 1614 (60.4) | 818 (46.5) | <0.001 |
| Tenofovir disoproxil fumarate | 234 (8.8) | 158 (9.0) | 0.829 |
| Lamivudine | 528 (19.8) | 465 (26.4) | <0.001 |
| Telbivudine | 141 (5.3) | 76 (4.3) | 0.155 |
| Adefovir dipivoxil | 178 (6.7) | 147 (8.3) | 0.039 |
| *Medication use at baseline (n, %)* | | | |
| Metformin | 1132 (42.4) | 0 (0) | <0.001 |
| Sulfonylureas | 1271 (47.6) | 474 (26.9) | <0.001 |
| DPP-4 inhibitor | 3 (0.1) | 1 (0.1) | 1.000 |
| Alpha glucosidase inhibitor | 41 (1.5) | 10 (0.6) | 0.004 |
| Insulin | 197 (7.4) | 331 (18.8) | <0.001 |
| Thiazolidinedione | 2 (0.1) | 3 (0.1) | 1.000 |
| Statin | 129 (4.8) | 102 (5.8) | 0.167 |
| ACEI or ARB | 499 (18.7) | 278 (15.8) | 0.014 |
| Beta blockers | 661 (24.8) | 728 (41.3) | <0.001 |
| Calcium channel blockers | 607 (22.7) | 385 (21.9) | 0.508 |
| Thiazide diuretics | 191 (7.2) | 80 (4.5) | <0.001 |
| Potassium-sparing diuretics | 261 (9.8) | 558 (31.7) | <0.001 |
| Loop diuretics | 220 (8.2) | 521 (29.6) | <0.001 |

**TABLE 2** (Continued)

| Clinical characteristics | Metformin user N = 2670 | Non-metformin users N = 1761 | *P* value |
|---|---|---|---|
| Aspirin or clopidogrel | 211 (7.9) | 199 (11.3) | <0.001 |
| NSAID | 407 (15.2) | 199 (11.3) | <0.001 |
| Follow-up duration from baseline (years) | 7.3 (3.9-11.5) | 2.6 (0.7-5.9) | <0.001 |

*Note:* Alanine aminotransferase and follow-up duration were expressed in median (interquartile range), whereas other continuous variables were expressed in mean ± SD. All comorbidities medications were represented as binary parameters. Qualitative and quantitative differences between groups were analyzed by chi-square or Fisher's exact tests for categorical parameters and Student's *t* test or Mann-Whitney test for continuous parameters, as appropriate.

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; $HbA_{1c}$, hemoglobin $A_{1c}$; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IQR, interquartile range; NA, nucleos(t)ide analogues; NSAID, nonsteroidal anti-inflammatory drug.

[a]Percentages were based on non-missing data.

**TABLE 3** The risk of metabolic acidosis in different Child-Pugh class and estimated glomerular filtration rate (eGFR) category as compared to patients in Child-Pugh class A and eGFR ≥90 mL/min/1.73 $m^2$

| Time-dependent eGFR category[a] (mL/min/1.73 $m^2$) | Child-Pugh class A[b] N = 5865 | | Child-Pugh class B[b] N = 9699 | | Child-Pugh class C[b] N = 3266 | |
|---|---|---|---|---|---|---|
| | aSHR (95% CI)[c] | *P* value | aSHR (95% CI)[c] | *P* value | aSHR (95% CI)[c] | *P* value |
| eGFR ≥90 N = 8422 | 1 | - | 3.50 (2.28-5.36) | <0.001 | 22.44 (14.11-35.69) | <0.001 |
| eGFR 60-89 N = 15 923 | 1.10 (0.72-1.68) | 0.675 | 3.88 (2.52-5.99) | <0.001 | 15.29 (9.09-25.72) | <0.001 |
| eGFR 45-59 N = 11 867 | 1.56 (0.96-2.53) | 0.073 | 9.51(6.11-14.82) | <0.001 | 18.26 (10.02-33.26) | <0.001 |
| eGFR 30-44 N = 7495 | 4.01 (2.46-6.54) | <0.001 | 15.88 (10.28-24.53) | <0.001 | 38.63 (23.29-64.06) | <0.001 |
| eGFR <30 N = 3209 | 21.35 (14.13-32.27) | <0.001 | 61.33 (40.98-91.79) | <0.001 | 86.16 (56.83-130.63) | <0.001 |

Abbreviations: aSHR, adjusted subdistribution hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

[a]The eGFR category of patients changed during follow-up. Including records at baseline, 46 916 records of change in eGFR category were collected during follow-up of the 4431 patients.

[b]The Child-Pugh class of patients changed during follow-up. Including records at baseline, 18 830 records of change in Child-Pugh class were collected during follow-up of the 4431 patients.

[c]Reference group was patients in Child-Pugh class A and eGFR ≥90 mL/min/1.73 $m^2$. Age, gender, use of anti-diabetic agents and other relevant medications, presence of hypertension, ischemic heart disease, congestive heart failure, cerebrovascular events, and renal replacement therapy during follow-up are adjusted as covariates.

patients with different severity of CKD and CHB-related liver cirrhosis. Our data suggest that both Child-Pugh class B cirrhosis or above and stage 3A CKD or above were independently associated with higher risks of metabolic acidosis to as much as 86 times. Meanwhile, metformin use was associated with an even higher risk in patients with Child-Pugh class B cirrhosis or above and stage 3A CKD or above.

Our result was mostly consistent with the current Food and Drug Administration recommendation that initiation of metformin is not recommended for patients with stage 3B CKD and is contraindicated in patients with stage 4 CKD or above, owing to the increased risk of metabolic acidosis.[26] Notably, our study demonstrated that metformin use should be cautioned in cirrhotic patients, especially those with stage 3A CKD or above, which is in contrast with some previous studies on patients with liver cirrhosis. A retrospective study on 172 diabetic subjects who continued metformin after diagnosis of cirrhosis reported no cases of lactic acidosis with a median follow-up of 5.2 years.[10] Another retrospective study consisting of 110 biopsy-proven non-alcoholic steatohepatitis patients with bridging fibrosis or cirrhosis who were on metformin also reported no occurrences of lactic acidosis.[12] Such disparate outcome may stem from several reasons and the low incidence of lactic acidosis is perhaps the most important one. Indeed, the estimated incidence of metformin-associated lactic acidosis is as low as around 0.03 per 1000 patient-years.[17] Studies with a limited number of subjects may not have adequate statistical power to identify the association. To our knowledge, our study is currently one of the largest retrospective study that evaluates the risk of metabolic acidosis in cirrhotic patients. Unlike previous studies, the

**TABLE 4** The association between the use of metformin and the risk of metabolic acidosis under different Child-Pugh class and estimated glomerular filtration rate (eGFR) category

| Time-dependent eGFR category[a] (mL/min/1.73 m$^2$) | Child-Pugh class A[b] N = 5865 | | Child-Pugh class B[b] N = 9699 | | Child-Pugh class C[b] N = 3266 | |
|---|---|---|---|---|---|---|
| | aHR (95% CI)[c] | *P* value | aHR (95% CI) [§] | *P* value | aHR (95% CI) [§] | *P* value |
| eGFR ≥90 N = 8422 | 0.82 (0.54-1.23) | 0.332 | 1.02 (0.66-1.56) | 0.935 | 1.00 (0.58-1.71) | 0.990 |
| eGFR 60–89 N = 15 923 | 0.87 (0.60-1.24) | 0.435 | 1.08 (0.72-1.62) | 0.717 | 1.06 (0.60-1.86) | 0.851 |
| eGFR 45–59 N = 11 867 | 1.34 (0.87-2.07) | 0.180 | 1.68 (1.13-2.48) | 0.010 | 1.64 (0.93-2.90) | 0.090 |
| eGFR 30-44 N = 7495 | 1.24 (0.79-1.96) | 0.349 | 1.55 (1.00-2.40) | 0.050 | 1.52 (0.82-2.80) | 0.182 |
| eGFR <30 N = 3209 | 1.97 (1.31–2.97) | 0.001 | 2.46 (1.67-3.63) | <0.001 | 2.41 (1.47-3.96) | <0.001 |

Abbreviations: aSHR, adjusted subdistribution hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

[a]The eGFR category of patients changed during follow-up. Including records at baseline, 46 916 records of change in eGFR category were collected during follow-up of the 4431 patients.

[b]The Child-Pugh class of patients changed during follow-up. Including records at baseline, 18 830 records of change in Child-Pugh class were collected during follow-up of the 4431 patients.

[c]Reference group was patients with no metformin use in the same Child-Pugh class and eGFR category. Age, gender, use of anti-diabetic agents and other relevant medications, presence of hypertension, ischemic heart disease, congestive heart failure, cerebrovascular events, and renal replacement therapy during follow-up are adjusted as covariates.

respectable sample size of our study allowed us to perform sub-group analysis with respect to patients' severity of cirrhosis and CKD to assess their combined associations. The interaction between metformin, end-stage CKD, and decompensated cirrhosis can be explained by the metabolism of lactate and metformin in human bodies. As metformin is a small molecule readily filtered in the glomerulus, as well as a substrate for several renal transporters including organic cation transporter 1 (OCT1), OCT2, and OCT3,[27] renal excretion of unchanged molecules is its major means of clearance. Reduced renal metformin clearance due to CKD leads to increased plasma metformin concentration, which was strongly associated with lactic acidosis.[28] While metformin use is generally safe and well-tolerated, previous studies indicated that a secondary event which alters lactate production or clearance may result in lactic acidosis.[28] In normal subjects, hepatic clearance of lactate can reach as much as 320 mmol/hour, which is far beyond normal rate of production.[29] In case of decompensated cirrhosis that impair lactate clearance, together with high plasma metformin concentration that inhibits mitochondrial oxidative metabolism, increasing lactate production via anaerobic pathway and reducing its clearance,[28] the risk of lactic acidosis significantly increases.

In contrast, it is worth to notice that metformin use in patients with cirrhosis, even Child-Pugh class C, but with CKD stage 2 or below (eGFR ≥60 mL/min/1.73 m$^2$) was not associated with an increased risk of metabolic acidosis compared to non-metformin users of the same Child-Pugh class and CKD stage. Such findings may be clinically relevant as metformin use may not further increase the risk of metabolic acidosis in cirrhotic patients without or with only mild renal impairment. Current evidence suggested that metformin use was associated with a wide range of benefits in diabetic patients even in those with comorbid liver diseases. In the United Kingdom Prospective Diabetes Study, metformin treatment reduced risk of myocardial infarction by 39% via its actions on the inflammatory, coagulation, and oxidative pathways.[30] In DM patients with or without cirrhosis, metformin was shown to reduce HCC incidence by regulating insulin growth factor 1, transcription nuclear factor-kappa B, and AMP-activated protein kinase pathway.[31] One retrospective study reported that continuing metformin after the diagnosis of cirrhosis significantly reduces mortality as compared to those who discontinued.[10] If future studies were consistent with our findings, metformin use might be considered in patients with cirrhosis with no or only mild renal impairment. Moreover, our study showed no statistically significant correlation between the daily metformin dose and risk of metabolic acidosis, implying that a dose adjustment alone may not be sufficient to reduce risk of metabolic acidosis in any sub-groups.

With the use of territory-wide data representing approximately 80% of the local population, our study has the advantages of a large sample size and long follow-up duration to detect uncommon events. Nonetheless, there are also a number of limitations. First, despite the relatively large sample size, our study may not be powered enough to examine the associations of metformin in some sub-groups, especially those with stage 4 CKD or above due to contraindication. Second, missing data and some errors in correctly identifying cirrhotic patients cannot be avoided as physicians may adopt different criteria to diagnose cirrhosis and this may affect the coding in CDARS. Liver biopsy is not a routine clinical practice and liver stiffness measurement is not readily available in all Hong Kong public hospitals. This is, however, partly compensated by our large sample size. Thirdly, owing to the retrospective nature of our study, we did not screen every patient for

**TABLE 5** The association between metformin maximum daily dose with risk of metabolic acidosis under different Child-Pugh class and estimated glomerular filtration rate (eGFR) category

| Time-dependent eGFR category[a] (mL/min/1.73 m$^2$) | Child-Pugh class Ab N = 5865 | | Child-Pugh class B[b] N = 9699 | | Child-Pugh class C[b] N = 3266 | |
|---|---|---|---|---|---|---|
| | aSHR (95% CI)[c] | *P* value | aSHR (95% CI)[c] | *P* value | aSHR (95% CI)[c] | *P* value |
| eGFR ≥90<br>N = 8422 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>1.22 (0.63-2.36)<br>Max. dose >1000 mg:<br>0.72 (0.46-1.14) | 0.562<br>0.157 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>1.64 (0.83-3.23)<br>Max. dose >1000 mg:<br>0.85 (0.52-1.38) | 0.151<br>0.509 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>1.95 (0.90-4.23)<br>Max. dose >1000 mg:<br>0.74 (0.38-1.47) | 0.091<br>0.394 |
| eGFR 60–89<br>N = 15 923 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>1.01 (0.57-1.80)<br>Max. dose >1000 mg:<br>0.81 (0.54-1.21) | 0.976<br>0.304 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>1.36 (0.74-2.51)<br>Max. dose >1000 mg:<br>0.96 (0.59-1.55) | 0.322<br>0.858 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>1.62 (0.71-3.67)<br>Max. dose >1000 mg:<br>0.84 (0.41-1.70) | 0.251<br>0.623 |
| eGFR 45–59<br>N = 11 867 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>1.12 (0.51-2.45)<br>Max. dose >1000 mg:<br>1.46 (0.91-2.34) | 0.781<br>0.120 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>1.51 (0.78-2.93)<br>Max. dose >1000 mg:<br>1.72 (1.11-2.66) | 0.223<br>0.015 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>1.79 (0.73-4.38)<br>Max. dose >1000 mg:<br>1.50 (0.74-3.05) | 0.201<br>0.257 |
| eGFR 30–44<br>N = 7495 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>1.02 (0.45-2.30)<br>Max. dose >1000 mg:<br>1.34 (0.81-2.20) | 0.966<br>0.252 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>1.37 (0.57-3.33)<br>Max. dose >1000 mg:<br>1.58 (0.98-2.54) | 0.482<br>0.058 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>1.63 (0.58-4.56)<br>Max. dose >1000 mg:<br>1.38 (0.66-2.90) | 0.351<br>0.391 |
| eGFR <30<br>N = 3209 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>2.45 (1.25-4.78)<br>Max. dose >1000 mg:<br>1.87 (1.15-3.02) | 0.009<br>0.011 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>3.30 (1.73-6.29)<br>Max. dose >1000 mg:<br>2.20 (1.39-3.49) | <0.001<br>0.001 | No metformin use:<br>Referent<br>Max. dose ≤1000 mg:<br>3.92 (1.73-8.86)<br>Max. dose >1000 mg:<br>1.93 (1.05-3.53) | 0.001<br>0.033 |

Abbreviations: aSHR, adjusted subdistribution hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

[a]The eGFR category of patients changed during follow-up. Including records at baseline, 46 916 records of change in eGFR category were collected during follow-up of the 4431 patients.

[b]The Child-Pugh class of patients changed during follow-up. Including records at baseline, 18 830 records of change in Child-Pugh class were collected during follow-up of the 4431 patients.

[c]Reference group was patients with no metformin use in the same Child-Pugh class and eGFR category. Age, gender, use of anti-diabetic agents and other relevant medications, presence of hypertension, ischemic heart disease, congestive heart failure, cerebrovascular events, and renal replacement therapy during follow-up are adjusted as covariates.

metabolic acidosis as of a systematic prospective screening study. On top of the use of diagnosis coding, we used the definition of blood pH ≤7.35 with lactate >5 mmol/L or arterial bicarbonate ≤18 mmol/L or venous bicarbonate ≤21 mmol/L to define the occurrence of metabolic acidosis. Furthermore, in a review in 2017, based on the presence of a secondary event that alters lactate production/ clearance and plasma metformin concentration, Lalau and his colleagues suggested classification for lactic acidosis in metformin-treated patients.[32] Metformin unrelated lactic acidosis, metformin associated lactic acidosis, and metformin induced lactic acidosis are defined to avoid confusion. However, we were not able to measure the plasma concentration of metformin, hence incapable of establishing a relationship between plasma metformin concentration and metabolic acidosis. In such context, we can only assess the association of metformin use and metabolic acidosis in metformin-treated patients, but not the other groups. Fourth, data on duration of DM and cirrhosis were not available as the baseline was defined as the date of first diagnosis of DM in the database in the period of from January 1, 2000 to December 31, 2017, which might or might not correspond to the actual date of diagnosis.

In conclusion, our data have offered further insight into the safety of metformin use in diabetic patients with liver cirrhosis and CKD. Metformin use should be cautioned in patients with Child-Pugh class B cirrhosis or above and stage 3A CKD or above. Dose adjustment may not be sufficient to ensure safety. To examine the overall risk and benefits of using metformin in cirrhotic DM patients, more clinical

studies are necessary. Meanwhile, use of metformin in cirrhotic patients should be based on individual assessment of the risks and benefits, taking into consideration the stage of CKD, Child-Pugh class, other risk factors, patients' preference as well as access to medical centers.

## FUNDING

No funding was obtained for this study.

## CONFLICT OF INTEREST

Terry Yip has served as an advisory committee member and a speaker for Gilead Sciences.

Vincent Wong has served as an advisory committee member for 3V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Janssen, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, TARGET-NASH, and Terns; and a speaker for Bristol-Myers Squibb, Echosens, Gilead Sciences, and Merck. He has also received a research grant from Gilead Sciences. Henry Chan is an advisor for AbbVie, Aptorum, Arbutus, Hepion, Intellia, Janssen, Gilead, GSK, GRAIL, Medimmune, Merck, Roche, Vaccitech, VenatoRx, Vir Biotechnology; and a speaker for Mylan, Gilead, and Roche. Grace Wong has served as an advisory committee member for Gilead Sciences, as a speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen, and Roche, and received research grant from Gilead Sciences. The other authors declare that they have no competing interests.

## AUTHOR CONTRIBUTIONS

Conceptualization: Grace Lai-Hung Wong, Vincent Wai-Sun Wong, Henry Lik-Yuen Chan

Formal Analysis: Terry Cheuk-Fung Yip, Raymond Ngai Chiu Chan

Funding Acquisition: Not applicable

Writing- Review and Editing: Terry Cheuk-Fung Yip, Raymond Ngai Chiu Chan, Vincent Wai-Sun Wong, Yee-Kit Tse, Lilian Yan Liang, Vicki Wing-Ki Hui, Xinrong Zhang, Guan-Lin Li, Henry Lik-Yuen Chan, Grace Lai-Hung Wong

Writing- Original Draft: Terry Cheuk-Fung Yip, Raymond Ngai Chiu Chan

## TRANSPARENCY STATEMENT

Manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Hospital Authority, Hong Kong. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from GLH Wong with the permission of the Hospital Authority, Hong Kong. Instructions on how to obtain a license can be obtained from the Hospital Authority, Hong Kong.

## ORCID

*Terry Cheuk-Fung Yip* https://orcid.org/0000-0002-1819-2464

## REFERENCES

1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas. *Diabetes Res Clin Pract*. 2019;157:107843.
2. American DA. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43 (suppl 1):S98-S110.
3. Murff HJ, Roumie CL, Greevy RA, et al. Metformin use and incidence cancer risk: evidence for a selective protective effect against liver cancer. *Cancer Causes Control*. 2018;29(9):823-832.
4. Campbell JM, Bellman SM, Stephenson MD, Lisy K. Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: a systematic review and meta-analysis. *Ageing Res Rev*. 2017;40:31-44.
5. Wang DS, Kusuhara H, Kato Y, Jonker JW, Schinkel AH, Sugiyama Y. Involvement of organic cation transporter 1 in the lactic acidosis caused by metformin. *Mol Pharmacol*. 2003;63(4):844-848.
6. Protti A, Russo R, Tagliabue P, et al. Oxygen consumption is depressed in patients with lactic acidosis due to biguanide intoxication. *Crit Care*. 2010;14(1):R22.
7. Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. *Biochem J*. 2000;348(Pt 3):607-614.
8. Lazarus B, Wu A, Shin JI, et al. Association of metformin use with risk of lactic acidosis across the range of kidney function: a community-based cohort study. *JAMA Intern Med*. 2018;178(7):903-910.
9. Brackett CC. Clarifying metformin's role and risks in liver dysfunction. *J Am Pharm Assoc*. 2010;50(3):407-410.
10. Zhang X, Harmsen WS, Mettler TA, et al. Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. *Hepatology*. 2014;60(6):2008-2016.
11. Vilar-Gomez E, Calzadilla-Bertot L, Wong VW, et al. Type 2 diabetes and metformin use associate with outcomes of patients with non-alcoholic steatohepatitis-related, Child-Pugh A cirrhosis. *Clin Gastroenterol Hepatol*. 2021;19(1):136-145.e6.
12. Vilar-Gomez E, Vuppalanchi R, Desai AP, et al. Long-term metformin use may improve clinical outcomes in diabetic patients with non-alcoholic steatohepatitis and bridging fibrosis or compensated cirrhosis. *Aliment Pharmacol Ther*. 2019;50(3):317-328.
13. Chen HP, Shieh JJ, Chang CC, et al. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. *Gut*. 2013;62(4):606-615.
14. Nkontchou G, Cosson E, Aout M, et al. Impact of metformin on the prognosis of cirrhosis induced by viral hepatitis C in diabetic patients. *J Clin Endocrinol Metab*. 2011;96(8):2601-2608.
15. Donadon V, Balbi M, Mas MD, Casarin P, Zanette G. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. *Liver Int*. 2010;30(5):750-758.
16. Tseng CH. Metformin and risk of hepatocellular carcinoma in patients with type 2 diabetes. *Liver Int*. 2018;38(11):2018-2027.
17. Bailey CJ, Turner RC. Metformin. *N Engl J Med*. 1996;334(9):574-579.
18. Cheng MCY, Tong YH, Kwok TC, et al. Development journey of clinical data analysis and reporting system (CDARS) in hospital authority of Hong Kong. *Medinfo*. 2010;1468-1468.
19. Yip TC, Chan HL, Wong VW, Tse YK, Lam KL, Wong GL. Impact of age and gender on risk of hepatocellular carcinoma after hepatitis B surface antigen seroclearance. *J Hepatol*. 2017;67(5):902-908.
20. Chan SL, Yip TC, Wong VW, et al. Pattern and impact of hepatic adverse events encountered during immune checkpoint inhibitors—a territory-wide cohort study. *Cancer Med*. 2020;9(19):7052-7061.

21. Yip TC, Wong GL, Wong VW, et al. Reassessing the accuracy of PAGE-B-related scores to predict hepatocellular carcinoma development in patients with chronic hepatitis B. *J Hepatol*. 2020;72(5):847-854.
22. Wong GL, Wong VW, Yuen BW, et al. An aging population of chronic hepatitis B with increasing comorbidities: a territory-wide study from 2000 to 2017. *Hepatology*. 2020;71(2):444-455.
23. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical Care in Diabetes-2018. *Diabetes Care*. 2018;41(suppl 1):S13-S27.
24. Wong JC, Chan HL, Tse YK, Yip TC, Wong VW, Wong GL. Statins reduce the risk of liver decompensation and death in chronic viral hepatitis: a propensity score weighted landmark analysis. *Aliment Pharmacol Ther*. 2017;46(10):1001-1010.
25. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.
26. Crowley MJ, Diamantidis CJ, McDuffie JR, et al. *Metformin use in patients with historical contraindications or precautions*. Washington, DC: VA Evidence-Based Synthesis Program Reports; 2016.
27. Tzvetkov MV, Vormfelde SV, Balen D, et al. The effects of genetic polymorphisms in the organic cation transporters OCT1, OCT2, and OCT3 on the renal clearance of metformin. *Clin Pharmacol Ther*. 2009;86(3):299-306.
28. Seidowsky A, Nseir S, Houdret N, Fourrier F. Metformin-associated lactic acidosis: a prognostic and therapeutic study. *Crit Care Med*. 2009;37(7):2191-2196.
29. Fall PJ, Szerlip HM. Lactic acidosis: from sour milk to septic shock. *J Intensive Care Med*. 2005;20(5):255-271.
30. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352(9131):854-865.
31. Fujita Y, Inagaki N. Metformin: new preparations and nonglycemic benefits. *Curr Diab Rep*. 2017;17(1):5.
32. Lalau JD, Kajbaf F, Protti A, Christensen MM, De Broe ME, Wiernsperger N. Metformin-associated lactic acidosis (MALA): moving towards a new paradigm. *Diabetes Obes Metab*. 2017;19(11):1502-1512.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Yip TC-F, Chan RNC, Wong VW-S, et al. Association of metformin use on metabolic acidosis in diabetic patients with chronic hepatitis B-related cirrhosis and renal impairment. *Health Sci Rep*. 2021;4:e352. https://doi.org/10.1002/hsr2.352