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Glucose-lowering drugs and outcome from COVID-19 among patients with type 2 diabetes mellitus: a population-wide analysis in Hong Kong

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ABSTRACT

Objectives To investigate the association between baseline use of glucose-lowering drugs and serious clinical outcome among patients with type 2 diabetes.

Design Territory-wide retrospective cohort of confirmed cases of COVID-19 between January 2020 and February 2021.

Setting All public health facilities in Hong Kong.

Participants 1220 patients with diabetes who were admitted for confirmed COVID-19.

Primary and secondary outcome measures Composite clinical endpoint of intensive care unit admission, requirement of invasive mechanical ventilation and/or in-hospital death.

Results In this cohort (median age 65.3 years, 54.3% men), 737 (60.4%) patients were treated with metformin, 385 (31.6%) with sulphonylureas, 199 (16.3%) with dipeptidyl peptidase-4 (DPP-4) inhibitors and 273 (22.4%) with insulin prior to admission. In multivariate Cox regression, use of metformin and DPP-4 inhibitors was associated with reduced incidence of the composite endpoint relative to non-use, with respective HRs of 0.51 (95% CI 0.34 to 0.77, p=0.001) and 0.46 (95% CI 0.29 to 0.71, p<0.001), adjusted for age, sex, diabetes duration, glycated haemoglobin (HbA1c), smoking, comorbidities and drugs. Use of sulphonylureas (HR 1.55, 95% CI 1.07 to 2.24, p=0.022) and insulin (HR 6.34, 95% CI 3.72 to 10.78, p<0.001) were both associated with increased hazards of the composite endpoint.

Conclusions Users of metformin and DPP-4 inhibitors had fewer adverse outcomes from COVID-19 compared with non-users, whereas insulin and sulphonylurea might predict a worse prognosis.

Strengths and limitations of this study

- This cohort study included over 95% of all patients with COVID-19 in Hong Kong in the study period.
- Statistical methods including multivariable adjustment and propensity score weighting have been adopted to adjust for important confounders of the clinical endpoints.
- The study is an observational retrospective cohort study with inherent limitations related to unmeasured confounding.
- The study is not able to infer causality given the likelihood of confounding by indication, for example, with respect to metformin and insulin use.
- We reported data in Chinese people and our results cannot be generalised to other ethnic groups.

INTRODUCTION

Patients with diabetes are more likely to have serious outcomes from coronavirus infections including severe acute respiratory syndrome (SARS), Middle-East respiratory syndrome (MERS) and COVID-19.[1–6] In a population-based analysis of in-hospital fatalities due to COVID-19 in the UK, type 1 diabetes and type 2 diabetes were associated with increased odds of 3.5 and 2.0 for death, adjusted for age, sex and sociodemographic factors.[6] The excess deaths might be related to co-occurrence of other medical conditions such as obesity and cardiovascular diseases that are independent risk factors for adverse outcomes.[7–10] Furthermore, diabetes gives rise to aberrant inflammatory responses which predispose to more intense lung infiltration, cytokine storm and multiorgan failure.[11] Proinflammatory indicators such as interleukin (IL)-6, IL-2 receptor, procalcitonin, tumour necrosis factor-α and C reactive protein (CRP) levels are generally higher in patients with diabetes compared with those without diabetes.[12]

Several glucose-lowering drug classes have immunomodulatory effects. Metformin activates AMP-activated protein kinase (AMPK) which in turn suppresses a number of inflammatory pathways including nuclear factor kappa B and mammalian target of rapamycin.[13 14] Activation of AMPK also stabilises ACE 2, the vasodilator effect of which improve organ blood flow and may protect against lung injury.[15] Both observational cohort and randomised controlled studies reported

reduced risks of pneumonia and other infections with metformin therapy.[16 17] Dipeptidyl peptidase-4 (DPP-4), also known as cluster of differentiation 26, is expressed in immune cells and is implicated in the regulation of adaptive immunity.[18] In a case–control study of patients with COVID-19, in-hospital treatment with sitagliptin was linked to improved survival and other measures of clinical outcome.[19] However, the beneficial effects of DPP-4 inhibitors have not been supported by other studies.[20–22] In a territory-wide retrospective cohort of confirmed cases of COVID-19 between January 2020 and February 2021, we investigated the association between baseline use of glucose-lowering drugs and serious clinical outcomes among patients with type 2 diabetes.

METHODS

Setting and patients

The Hong Kong Hospital Authority (HA) governs all public hospitals and general outpatient departments in the territory and provides care for approximately 80% of local residents.[23] Given the high cost differential in healthcare between the public and private sector with the private sector being significantly more expensive, people who use health services in the private sector are usually at a more favourable socioeconomic position. Since the beginning of the pandemic, all cases of COVID-19, including symptomatic cases presented to outpatient clinics or hospitals, asymptomatic contacts of confirmed cases and inbound travellers, were admitted to HA healthcare facilities. Clinical data including past medical diagnoses, drug prescription records, laboratory results, admission records and vital status were captured in the Clinical Data Analysis and Reporting System (CDARS), an electronic medical record system used in the Hong Kong HA. We retrieved data of all patients presented with COVID-19 who admitted between 23 January 2020 (the first case in Hong Kong) and 28 February 2021.[24] All patient data were anonymised to ensure confidentiality. Patients aged below 18 years were excluded.

Data collection

Patients with COVID-19 were identified based on positive SARS-CoV-2 PCR in nasopharyngeal swab in any one of the HA laboratories.[25] For each patient, we obtained demographic data (age, sex), relevant diagnoses using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, drug prescription record for at least 12 months before admission, laboratory results for plasma glucose, glycated haemoglobin (HbA1c) and lipid profile for at least 12 months before admission, as well as plasma glucose, kidney function, liver function, inflammatory markers, haematology and coagulation study on the day of admission. Progress during admission including treatment with corticosteroid, intravenous immunoglobulin, antiviral therapy, antifungal therapy, antibiotic therapy, mechanical ventilation and transfer to intensive care unit (ICU) were also retrieved. Patients were followed from the date of diagnosing COVID-19 until discharge from hospital or death. Data capture was censored on 24 April 2021.

Definition and outcome

A patient was classified to have type 2 diabetes if he or she fulfilled one or more of the following criteria within 12 months before admission: use of non-insulin glucose-lowering drugs for at least 1 day, continuous use of insulin for ≥28 days, HbA1c ≥6.5% in any one measurement, fasting plasma glucose ≥7.0 mmol/L in any one measurement and/or diagnosis code of type 2 diabetes based on ICD-9-CM.

Baseline use of glucose-lowering drugs, including metformin, sulphonylureas (glibenclamide, gliclazide, glimepiride, glipizide), DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) and insulin, was identified based on prescription record of the respective drug. Patients were considered to be baseline users if a prescription record was found within 12 months before and up to the day of admission. Patients were considered to be non-users if a prescription record was not found within 12 months before admission, on the day of and during admission. We have not set a minimum exposure time to define users because patients who attended the private sector for diabetes treatment would not have any prescription records in the HA CDARS before admission, but they would have a prescription record on the day of admission indicating their preadmission use of the drug. The proportion of patients receiving medical care in the private sector is around 10%.[23]

Relevant comorbidities were identified as follows: hypertension was defined as the use of blood pressuring lowering drugs within 12 months before admission and/or ICD-9-CM code of hypertension (online supplemental table 1); chronic kidney disease was defined as having an estimated glomerular filtration rate <60 mL/min/1.73 m^2 as determined using the Chronic Kidney Disease Epidemiology Collaboration equation within 12 months prior to admission and/or ICD-9-CM codes of kidney diseases (online supplemental table 1); chronic liver disease, coronary heart disease, congestive heart failure, cerebrovascular disease, chronic obstructive airway disease and cancer were defined based on ICD-9-CM codes (online supplemental table 1). The use of ICD-9-CM codes in CDARS to identify medical conditions has been shown to be 99% accurate when referenced to clinical, laboratory, imaging and endoscopy results from the electronic medical records.[26] Clinical endpoints included ICU admission, mechanical ventilation, in-hospital death and composite endpoint of ICU admission, mechanical ventilation and/or in-hospital death. For the composite endpoint, patients were followed from the date of diagnosing COVID-19 until the date of ICU admission, use of mechanical ventilation, in-hospital death or discharge from hospital, whichever came first. For the individual clinical endpoint, patients were followed from the date of diagnosing COVID-19

until the date of the occurrence of that individual clinical endpoint or discharge from hospital, whichever came first.

Statistical analysis

Analysis was conducted using R software (V.4.0.0). Continuous variables were expressed as mean±SD or median (IQR), as appropriate, and categorical variables as number (percentages). Between-group comparison was conducted by χ^2 test for categorical variables, Student's t-test for normally distributed continuous variables, and Kruskal-Wallis test for continuous variables with skewed distribution. Clinical characteristics were compared between users and non-users of metformin, sulphonylureas (glibenclamide, gliclazide, glimepiride, glipizide), DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) and insulin. Due to small number, use of thiazolidinediones, glucagon-like peptide-1 receptor agonists and sodium-glucose transport protein 2 inhibitors were not tested. Multivariate Cox regression was conducted to derive the HRs and 95% CIs of use versus non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin for primary and secondary clinical endpoints. The multivariate Cox model was adjusted for age, sex, diabetes duration, smoking, HbA1c, comorbidities (history of hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease and cancer), baseline use of other glucose-lowering drugs, statins and renin–angiotensin–aldosterone system (RAAS) inhibitors and in-hospital use of other glucose-lowering drugs. The multivariate Cox regression was limited to patients with available HbA1c measurement (n=886) in whom the latest HbA1c obtained within 12 months of hospital admission was used. The selection of variables was based on known or possible link between these variables and clinical endpoints. Due to the small proportion of patients with available data on body mass index (BMI) (9.3%), BMI was not included in the multivariate Cox regression model. In a sensitivity analysis, we generated propensity scores for glucose-lowering drug use using logistic regression model that contained age, sex, smoking, diabetes duration, comorbidities and baseline use of other glucose lowering drugs, statins and RAAS inhibitors using the overlap propensity score weighting method.[27] The weights were included in the multivariate Cox models to balance the differences in patient characteristics between glucose-lowering drug use groups. We also repeated the multivariate Cox regression excluding patients whose diabetes status was established by a single fasting plasma glucose measurement only, as these patients might not have diabetes.

Patient and public involvement

There was no patient of public involvement.

RESULTS

Baseline clinical characteristics by glucose lowering drug classes

Of 9839 adult patients with COVID-19, 1220 patients (12.4%) had type 2 diabetes. Patients with diabetes were older, had a male preponderance and higher frequencies of comorbidities than those without diabetes (online supplemental table 2). In patients with diabetes, 737 (60.4%) were treated with metformin, 385 (31.6%) with sulphonylureas, 199 (16.3%) with DPP-4 inhibitors and 273 (22.4%) with insulin at baseline. Generally, users of each of the glucose-lowering drug class had longer diabetes duration and higher HbA1c levels than non-users of the respective drug class, whereas BMI did not differ (table 1). Metformin users were younger and users of insulin and DPP-4 inhibitors were older than their respective non-users, while no age difference was detected between users and non-users of sulphonylureas (table 1). Coronary heart disease and heart failure were less common in metformin users and more common in insulin users when compared with their respective non-users (table 1). Chronic kidney disease was also less common in metformin users but more prevalent among users than non-users of other glucose-lowering drug classes (table 1).

Markers of disease severity and outcome by glucose lowering drug classes

On admission, random plasma glucose levels were higher in users than non-users of most oral glucose-lowering drugs, except for DPP-4 inhibitors (online supplemental table 3). In addition, metformin users had higher lymphocyte count, lower alkaline phosphatase levels and lactate dehydrogenase (LDH) levels than metformin non-users (online supplemental table 3). Users of sulphonylureas had higher CRP levels and total white cell count, and users of DPP-4 inhibitors had higher total white cell count compared with respective non-users (online supplemental table 3). Insulin users had higher plasma glucose levels, higher levels of most inflammatory markers including LDH, CRP, erythrocyte sedimentation rate and procalcitonin, and lower lymphocyte count than insulin non-users (online supplemental table 3).

There were overall no differences in the proportion of patients receiving most types of antimicrobial therapy, corticosteroid and intravenous immunoglobulin between users and non-users of metformin, sulphonylureas and DPP-4 inhibitors, with the exception of less frequent administration of antibiotics among metformin users and more frequent use of antifungal therapy among users of sulphonylureas and DPP-4 inhibitors (online supplemental table 3). Insulin users were more likely to be treated with antimicrobial therapy and corticosteroid than non-users (online supplemental table 3).

During admission, 235 patients (19.3%) developed composite primary endpoint, 187 patients (15.3%) were transferred to ICU, 110 patients (9.0%) required mechanical ventilation, and 90 patients (7.4%) died. Fewer

Table 1 Clinical characteristics of patients with type 2 diabetes according to preadmission use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin

	Metformin			Sulphonylureas			DPP-4 inhibitors			Insulin		
	Users	Non-users	P value	Users	Non-users	P value	Users	Non-users	P value	Users	Non-users	P value
No	737	254		385	679		199	952		385	679	
Demographics												
Age, years	65.6 (57.7, 72.6)	68.9 (61.3, 79.7)	<0.001	66.0 (58.5, 73.1)	65.3 (57.3, 73.6)	0.656	67.0 (58.4, 75.5)	65.1 (56.8, 72.2)	0.029	66.0 (58.5, 73.1)	65.3 (57.3, 73.6)	0.656
Men, n (%)	405 (55.0)	131 (51.6)	0.391	222 (57.7)	350 (51.5)	0.063	118 (59.3)	506 (53.2)	0.133	222 (57.7)	350 (51.5)	0.063
Ex-/active smoker, n (%)	125 (17.0)	49 (19.3)	0.443	70 (18.2)	113 (16.6)	0.687	34 (17.1)	163 (17.1)	0.818	70 (18.2)	113 (16.6)	0.687
Metabolic parameters												
Diabetes duration, years	1.8 (1.4, 6.4)	1.2 (0.5, 2.5)	<0.001	1.8 (1.4, 7.6)	1.3 (0.0, 1.9)	<0.001	3.9 (1.5, 11.3)	1.4 (0.0, 1.9)	<0.001	1.8 (1.4, 7.6)	1.3 (0.0, 1.9)	<0.001
BMI, kg/m^2	24.1 (21.5, 27.7)	23.7 (22.2, 27.0)	0.670	24.4 (21.8, 27.8)	23.5 (21.5, 27.0)	0.382	25.0 (18.7, 27.0)	23.3 (21.6, 27.4)	0.636	22.9 (19.8, 25.9)	24.4 (22.2, 27.4)	0.051
HbA1c, %	7.3 (6.6, 8.5)	6.6 (6.1, 7.8)	<0.001	7.7 (6.9, 9.1)	6.9 (6.4, 8.2)	<0.001	7.6 (6.8, 8.9)	7.2 (6.5, 8.9)	0.027	7.7 (6.9, 9.1)	6.9 (6.4, 8.2)	<0.001
LDL-C, mmol/L	2.1 (1.7, 2.7)	2.4 (1.7, 3.0)	0.004	2.1 (1.7, 2.6)	2.2 (1.7, 2.8)	0.081	2.0 (1.5, 2.5)	2.3 (1.7, 2.8)	<0.001	2.1 (1.7, 2.6)	2.2 (1.7, 2.8)	0.081
HDL-C, mmol/L	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	0.857	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	0.17	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	0.311	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	0.17
Triglyceride, mmol/L	1.3 (0.9, 1.9)	1.4 (1.0, 2.0)	0.093	1.3 (1.0, 1.9)	1.36 (0.9, 2.0)	0.666	1.4 (1.0, 1.9)	1.4 (1.0, 2.0)	0.774	1.3 (1.0, 1.9)	1.36 (0.9, 2.0)	0.666
Comorbidities, n (%)												
Hypertension	465 (63.1)	144 (56.7)	0.083	267 (69.4)	329 (48.5)	<0.001	123 (61.8)	498 (52.3)	0.018	267 (69.4)	329 (48.5)	<0.001
Coronary heart disease	76 (10.3)	48 (18.9)	0.001	45 (11.7)	79 (11.6)	1	30 (15.1)	96 (10.1)	0.054	45 (11.7)	79 (11.6)	1
Heart failure	22 (3.0)	22 (8.7)	<0.001	13 (3.4)	29 (4.3)	0.578	11 (5.5)	32 (3.4)	0.208	13 (3.4)	29 (4.3)	0.578
Cerebrovascular disease	66 (9.0)	40 (15.7)	0.004	31 (8.1)	72 (10.6)	0.213	26 (13.1)	82 (8.6)	0.068	31 (8.1)	72 (10.6)	0.213
Chronic kidney disease	144 (19.5)	96 (37.8)	<0.001	98 (25.5)	135 (19.9)	0.042	72 (36.2)	164 (17.2)	<0.001	98 (25.5)	135 (19.9)	0.042
Chronic liver disease	26 (3.5)	17 (6.7)	0.05	16 (4.2)	27 (4.0)	1	9 (4.5)	34 (3.6)	0.661	16 (4.2)	27 (4.0)	1
COPD	39 (5.3)	19 (7.5)	0.26	23 (6.0)	35 (5.2)	0.671	10 (5.0)	50 (5.3)	1	23 (6.0)	35 (5.2)	0.671
Cancer	41 (5.6)	35 (13.8)	<0.001	18 (4.7)	58 (8.5)	0.026	12 (6.0)	70 (7.4)	0.611	18 (4.7)	58 (8.5)	0.026
Baseline drug use, n (%)												
Metformin	737 (100.0)	0 (0.0)	<0.001	352 (91.4)	343 (50.5)	<0.001	169 (84.9)	534 (56.1)	<0.001	352 (91.4)	343 (50.5)	<0.001
Sulphonylureas	352 (47.8)	27 (10.6)	<0.001	385 (100.0)	0 (0.0)	<0.001	123 (61.8)	240 (25.2)	<0.001	385 (100.0)	0 (0.0)	<0.001

Continued

Table 1 Continued

	Metformin			Sulphonylureas			DPP-4 inhibitors			Insulin		
	Users	Non-users	P value	Users	Non-users	P value	Users	Non-users	P value	Users	Non-users	P value
No	737	254		385	679		199	952		385	679	
DPP-4 inhibitors	169 (22.9)	28 (11.0)	<0.001	123 (31.9)	71 (10.5)	<0.001	199 (100.0)	0 (0.0)	<0.001	123 (31.9)	71 (10.5)	<0.001
Thiazolidine-diones	84 (11.4)	6 (2.4)	<0.001	58 (15.1)	31 (4.6)	<0.001	39 (19.6)	50 (5.3)	<0.001	58 (15.1)	31 (4.6)	<0.001
SGLT-2 inhibitors	70 (9.5)	8 (3.2)	0.002	37 (9.6)	41 (6.0)	0.043	41 (20.6)	34 (3.6)	<0.001	37 (9.6)	41 (6.0)	0.043
GLP1 receptor agonists	11 (1.5)	2 (0.8)	0.533	4 (1.0)	9 (1.3)	0.779	4 (2.0)	8 (0.8)	0.138	4 (1.0)	9 (1.3)	0.779
Insulin	208 (28.2)	49 (19.3)	0.007	120 (31.2)	129 (19.0)	<0.001	99 (49.7)	157 (16.5)	<0.001	120 (31.2)	129 (19.0)	<0.001
Statins	546 (74.1)	138 (54.3)	<0.001	294 (76.4)	379 (55.8)	<0.001	153 (76.9)	528 (55.5)	<0.001	294 (76.4)	379 (55.8)	<0.001
BP lowering drugs	473 (64.2)	165 (65.0)	0.882	250 (64.9)	381 (56.1)	0.006	129 (64.8)	529 (55.6)	0.02	250 (64.9)	381 (56.1)	0.006
RAAS inhibitors	440 (59.7)	126 (49.6)	0.006	248 (64.4)	303 (44.6)	<0.001	134 (67.3)	428 (45.0)	<0.001	248 (64.4)	303 (44.6)	<0.001

Data are presented as mean±SD or median (IQR) for continuous variables, and number (percentage) for categorical variables.
BMI, body mass index; BP, blood pressure; COPD, chronic obstructive airway disease; DPP-4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide 1; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RAAS, renin–angiotensin–aldosterone system; SGLT-2, sodium glucose co-transporter-2.

metformin users reached composite endpoint (proportions: 17.2% vs 27.6%, p=0.001; incidence rates: 4914.1 vs 6633.4 per 1000 person-year, p=0.043) or died (proportions: 6.0% vs 17.3%, p<0.001; incidence rates: 1258.8 vs 2946.5 per 1000 person-year, p<0.001) compared with non-users (table 2, online supplemental table 4). Users of sulphonylureas and insulin were more likely than non-users to reach composite endpoint, required ICU admission and mechanical ventilation, and insulin users were also more likely to die than non-users (table 2, online supplemental table 4). The proportion of patients developing primary or secondary endpoints were similar between users and non-users of DPP-4 inhibitors (table 2, online supplemental table 4).

Association between preadmission use of glucose lowering drugs and clinical outcome

In multivariate Cox regression model, baseline use of metformin was associated with reduced hazards of composite endpoint of ICU admission, mechanical ventilation and/or in-hospital death (adjusted HR 0.51 (95% CI 0.34 to 0.77), p=0.001) and individual endpoints of ICU admission (adjusted HR 0.53 (95% CI 0.33 to 0.86), p=0.010), mechanical ventilation (adjusted HR 0.51 (95% CI 0.27 to 0.97), p=0.041) and in-hospital death (adjusted HR 0.51 (95% CI 0.27 to 0.97), p=0.039) relative to non-use (table 3). Baseline use of DPP-4 inhibitors was associated with reduced hazards of composite endpoint (adjusted HR 0.46 (95% CI 0.29 to 0.71), p<0.001) and ICU admission (adjusted HR 0.45 (95% CI 0.28 to 0.74). p=0.002) (table 3). Use of sulphonylureas (adjusted HR 1.55 (95% CI 1.07 to 2.24), p=0.022) and insulin (adjusted HR 6.34 (95% CI 3.72 to 10.78), p<0.001) were both associated with increased hazards of the composite endpoint (table 3). Sensitivity analysis using multivariate Cox regression with propensity score weighting yielded similar findings (online supplemental table 5). Exclusion of patients who were identified as having diabetes based on a single fasting plasma glucose measurement (n=25) had minimal effect on the results (online supplemental table 6).

DISCUSSION

In a territory-wide cohort of patients with diabetes presented with COVID-19, we showed that preadmission use of metformin and DPP-4 inhibitors was linked to reduced risks of serious outcome, whereas the use of sulphonylureas and insulin was associated with a worse prognosis. Our findings corroborate and extend the results of previous studies and suggest a possible protective role of metformin and DPP-4 inhibitors against severe respiratory tract infection. The strength of our study includes the unbiased nature of the cohort as the database captured all patients with COVID-19 in Hong Kong. Both symptomatic and asymptomatic patients were admitted to healthcare facilities and their clinical data were included in the present analysis. Furthermore,

Table 2 Clinical outcome from COVID-19 according to baseline use or non-use of metformin, sulphonylureas, DPP-4 inhibitors and insulin

	Metformin			Sulphonylureas			DPP-4 inhibitors			Insulin		
	Users	Non-users	P value	Users	Non-users	P value	Users	Non-users	P value	Users	Non-users	P value
ICU admission, n (%)	108 (14.7)	43 (16.9)	0.442	79 (20.5)	79 (11.6)	<0.001	32 (16.1)	136 (14.3)	0.588	76 (27.8)	17 (2.7)	<0.001
Mechanical ventilation, n (%)	67 (9.1)	24 (9.5)	0.965	51 (13.2)	43 (6.3)	<0.001	22 (11.1)	78 (8.2)	0.244	51 (18.7)	4 (0.6)	<0.001
In-hospital death, n (%)	44 (6.0)	44 (17.3)	<0.001	35 (9.1)	47 (6.9)	0.248	18 (9.1)	71 (7.5)	0.538	32 (11.7)	22 (3.5)	<0.001
ICU admission, mechanical ventilation and/or in-hospital death, n (%)	127 (17.2)	70 (27.6)	0.001	91 (23.6)	109 (16.1)	0.003	40 (20.1)	175 (18.4)	0.642	88 (32.2)	35 (5.6)	<0.001

DPP-4, dipeptidyl peptidase-4; ICU, intensive care unit.

the use of a universal electronic medical record for drug prescription ensures that we have accurately classified use and non-use of different glucose-lowering drug classes.

Metformin, infection and COVID-19

Several observational studies in patients hospitalised with COVID-19 reported the association between metformin use and death and other measures of adverse outcome.[22 28–31] In a nationwide study conducted in England including 2.85 million patients with type 2 diabetes among whom 13 479 had a record of COVID-19-related deaths, those prescribed metformin had fewer deaths with adjusted HR 0.77 when compared with those not prescribed metformin.[22] In another study of 6256 patients (mean age 75 years) with either type 2 diabetes or obesity admitted with COVID-19 in the USA, metformin use was found to reduce the risk of death in women with HR 0.79 adjusted for age and comorbidities although no effect was observed in men.[28] Two meta-analyses also noted a protective effect of metformin with pooled ORs of around 0.6 for mortality from COVID-19.[32 33] However, in an analysis of 1317 patients (mean age 70 years) with COVID-19 and diabetes in France, metformin was associated with fewer deaths in univariate but not in multivariate analysis.[7] Similarly, among 1297 patients (mean age 75 years) with diabetes hospitalised for COVID-19 in Spain, the group on metformin were less likely to die and/or require ICU admission or mechanical ventilation than non-users, but no difference was detected when the two groups were propensity matched for demographics, comorbidities and drugs.[20] In this study, we found that metformin was associated with 50% reduction in the risk of in-hospital deaths and 50% reduction in the risk of composite clinical endpoint. The inconsistency in findings between studies could be due to a number of factors, including but not limited to differences in age and disease characteristics of the patient cohorts and in the statistical methods used to examine drug effects. One of the limitations of our study is the high proportion of patients with missing information on anthropometric measures and we did not include these variables in multivariate adjustment. Previous studies have reported a U-shape relationship between BMI and deaths from COVID-19 in people with and without diabetes.[34 35] Obesity alters the mechanics of the lungs and chest wall which increases the susceptibility to respiratory failure during infection. Furthermore, confounding by indication remained an important source of bias in our study as patients who were not prescribed metformin might have other medical conditions, for example, malnutrition, kidney or liver diseases, that contraindicated the use of metformin and conferred a poorer prognosis from COVID-19.[36] Nonetheless, our results are in line with most other studies suggesting possible benefits of metformin, or at least no evidence of harm, in patients with type 2 diabetes afflicted by COVID-19.

The immunomodulatory action of metformin has been demonstrated in cell and animal models as well as in

Table 3 Multivariate Cox regression for the association between baseline use of glucose lowering drugs and clinical outcome

	Metformin		Sulphonylureas		DPP-4 inhibitors		Insulin	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
ICU admission	0.53 (0.33 to 0.86)	0.01	1.45 (0.96 to 2.19)	0.074	0.45 (0.28 to 0.74)	0.002	10.95 (5.5 to 21.8)	<0.001
Mechanical ventilation	0.51 (0.27 to 0.97)	0.041	1.35 (0.78 to 2.36)	0.286	0.57 (0.29 to 1.11)	0.098	21.99 (4.85 to 99.6)	<0.001
In-hospital death	0.51 (0.27 to 0.97)	0.039	2.42 (1.25 to 4.7)	0.009	0.70 (0.35 to 1.39)	0.304	2.86 (1.09 to 7.48)	0.033
ICU admission, mechanical ventilation and/or in-hospital death	0.51 (0.34 to 0.77)	0.001	1.55 (1.07 to 2.24)	0.022	0.46 (0.29 to 0.71)	<0.001	6.34 (3.72 to 10.78)	<0.001

Adjusted for age, sex, smoking, diabetes duration, HbA1c level, comorbidities (hypertension, coronary heart disease, heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive airway disease, cancer), preadmission use of other glucose-lowering drugs, statins and RAAS inhibitors, and in-hospital use of other glucose-lowering drugs.
DPP-4, dipeptidyl peptidase-4; HbA1c, glycated haemoglobin; ICU, intensive care unit; RAAS, renin–angiotensin–aldosterone system.

human studies, and is independent of the metabolic function of the drug.[13] In a recent randomised control trial of 53 patients taking systemic glucocorticoid for inflammatory diseases, those assigned metformin had reduced levels of high sensitivity CRP and neutrophil counts, accompanied by lower frequencies of pneumonia and moderate-to-severe infection than the placebo arm over a 12-week period.[37] In this study, metformin users had lower LDH levels and higher lymphocyte counts on admission than non-users. In infected patients, metformin may dampen the exaggerated immune reaction to SARS-CoV-2 which is causal for the development of severe lung injury and cytokine storms associated with type 2 diabetes.[11]

DPP-4 inhibitors and COVID-19

Dipeptidyl-peptidase-4 inhibitors have pleiotropic effects on the immune system and the effect of this drug class as an ancillary treatment of inflammatory diseases such as rheumatoid arthritis and viral infections have been previously examined.[18] Moreover, DPP-4 is a known receptor for MERS-CoV in human. It has been speculated that DPP-4 may also mediate the entry of SARS-CoV-2, although the evidences for this are yet to be consolidated.[38 39] In an Italian study of 338 patients with diabetes admitted with COVID-19, in-hospital initiation of sitagliptin reduced deaths by 56% and ICU admission by 49%.[19] Another case series in Italy including 90 patients with diabetes reported fewer COVID-19-related deaths among prevalent users of DPP-4 inhibitors adjusted for age and sex.[40] In this study, baseline use of DPP-4 inhibitors was associated with reduced risk of composite clinical endpoint although in-hospital deaths were not reduced. Notably, several observational studies and a meta-analysis did not find an association between DPP-4 inhibitors and complications from COVID-19.[20 21 41] In particular, in the large study conducted in England, COVID-19-related-deaths occurred more frequently in patients prescribed DPP-4 inhibitors.[22] Differences in statistical procedures may account for the inconsistent findings. Further studies are needed to investigate whether long-term exposure of this drug class can improve prognosis of coronavirus infection.

Insulin and COVID-19

We revealed a positive relationship between pre-admission insulin use and composite clinical outcome, driven mainly by increased hazards for ICU admission and mechanical ventilation among insulin users. Our results are consistent with several other studies suggesting that insulin use may predict a worse outcome from COVID-19.[20 42] Insulin therapy is usually initiated late in the diabetes continuum and it is very possible that the positive association between insulin use and adverse outcome was due to incomplete statistical removal of confounding by indication. In this study, insulin users were significantly older and were more likely to have premorbid kidney and cardiovascular diseases. On admission, insulin users also had higher inflammatory markers and lower lymphocyte counts which are important severity indicators. Although insulin therapy is deemed the most appropriate glucose-lowering option during acute illnesses, high level of vigilance should be maintained in managing patients on chronic insulin therapy who have a greater likelihood of deterioration.

Sulphonylurea and COVID-19

The risk association between sulphonylureas and in-hospital death was less expected and not well explained. In Hong Kong, sulphonylureas is widely prescribed as a second-line drug after metformin. In the present cohort, the frequencies of comorbidities were mostly balanced between users and non-users of sulphonylureas with the exception of a higher prevalence of chronic kidney disease among users. Previous studies on COVID-19 did

not show harm associated with sulphonylurea use. Glyburide has been shown to suppress the immune system but studies on the use of sulphonylurea with infection outcome have produced mixed results.[43]

LIMITATIONS

We acknowledge the following limitations. This was an observational cohort study with inherent limitations related to unmeasured confounding. Metabolic parameters including BMI were not available in a large proportion of patients and these variables were not included in the statistical adjustment. Among people with available BMI data, the mean BMI did not differ between users and non-users of glucose-lowering drug classes. Hence, we would speculate that the lack of adjustment for BMI in the Cox regression would not have made significant impact on the results. Despite statistical efforts to adjust for comorbidities, we could not fully address residual confounding by drug indication. In this connection, our results cannot be taken to infer causality between drug use and clinical outcome. Although we have included over 95% of all patients with COVID-19 in Hong Kong, the size of our cohort was relatively small. We reported data in Chinese people and our results cannot be generalised to other ethnic groups.

CONCLUSION

In this retrospective cohort of Chinese with type 2 diabetes, background use of metformin and DPP-4 inhibitors was associated with fewer complications of COVID-19, whereas insulin and sulphonylureas predicted a worse prognosis. Given the increased risk for serious infection in patients with diabetes, drugs with off-target action in immune pathways could be further evaluated for potential new application beyond the ambit of their original indication and assessed for use in modifying outcome from infectious diseases.

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