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Association Between Metformin Use and Mortality among Patients with Type 2 Diabetes Mellitus Hospitalized for COVID-19 Infection

Angeli Nicole Ong,[1] Ceryl Cindy Tan,[1] Maria Teresa Cañete,[2] Bryan Albert Lim,[3] Jeremyjones Robles[1,4]

[1]*Section of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, Chong Hua Hospital, Cebu City, Philippines*
[2]*Section of Neurology, Department of Internal Medicine, Chong Hua Hospital, Cebu City, Philippines*
[3]*Section of Infectious Diseases, Department of Internal Medicine, Chong Hua Hospital, Cebu City, Philippines*
[4]*Department of Internal Medicine, Cebu Institute of Medicine – Cebu Velez General Hospital, Cebu City, Philippines*

Abstract

Introduction. Metformin has known mechanistic benefits on COVID-19 infection due to its anti-inflammatory effects and its action on the ACE2 receptor. However, some physicians are reluctant to use it in hypoxemic patients due to potential lactic acidosis. The primary purpose of the study was to determine whether metformin use is associated with survival. We also wanted to determine whether there is a difference in outcomes in subcategories of metformin use, whether at home, in-hospital, or mixed home/in-hospital use.

Objectives. This study aimed to determine an association between metformin use and mortality among patients with type 2 diabetes mellitus hospitalized for COVID-19 infection.

Methodology. This was a cross-sectional analysis of data acquired from the COVID-19 database of two tertiary hospitals in Cebu from March 1, 2020, to September 30, 2020. Hospitalized adult Filipino patients with type 2 diabetes mellitus who tested positive for COVID-19 via RT-PCR were included and categorized as either metformin users or metformin non-users.

Results. We included 355 patients with type 2 diabetes mellitus in the study, 186 (52.4%) were metformin users. They were further categorized into home metformin users (n=109, 30.7%), in-hospital metformin users (n=40, 11.3%), and mixed home/in-hospital metformin users (n=37, 10.4%). Metformin use was associated with a lower risk for mortality compared to non-users (p=0.001; OR=0.424). In-hospital and mixed home/in-hospital metformin users were associated with lower mortality odds than non-users (p=0.002; OR=0.103 and p=0.005; OR 0.173, respectively). The lower risk for mortality was noted in metformin, regardless of dosage, from 500 mg to 2 g daily (p=0.002). Daily dose between ≥1000 mg to <2000 mg was associated with the greatest benefit on mortality (p≤0.001; OR=0.252). The survival distributions between metformin users and non-users were statistically different, showing inequality in survival ($\chi 2$=5.67, p=0.017).

Conclusion. Metformin was associated with a lower risk for mortality in persons with type 2 diabetes mellitus hospitalized for COVID-19 disease compared to non-users. Use of metformin in-hospital, and mixed home/in-hospital metformin use, was also associated with decreased risk for mortality. The greatest benefit seen was in those taking a daily dose of ≥1000 mg to <2000 mg.

Key words: metformin, diabetes mellitus, COVID-19, mortality

INTRODUCTION

In December 2019, the SARS-CoV-2 infection, which initially started in China, spread internationally and was declared a pandemic.[1] In over a year since its discovery, cases have reached more than 200 million globally, with more than four million deaths worldwide.[2] The Philippines has more than two million cases confirmed, with nearly forty thousand deaths attributed to the virus.[3]

The lungs are the primary target due to the high expression of the ACE2 receptor, which serves as its entry point.[4-6] The virus induces a cytokine storm causing alveolar epithelial damage, and in severe cases, may lead to acute respiratory disease syndrome and death.[7]

The most prevalent comorbid conditions noted with COVID-19 infection are hypertension, diabetes mellitus, cardiovascular disease, and obesity.[8,9] Studies also show that type 2 diabetes mellitus (T2DM) is a risk factor for more severe disease and is associated with an increased mortality rate.[10-13] Persons with diabetes have a greater risk for viral infection, adverse clinical outcomes, and mortality, as noted in previous coronavirus epidemics, namely

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Corresponding author: Angeli Nicole S. Ong, MD
Section of Endocrinology, Diabetes and Metabolism,
Department of Internal Medicine, Chong Hua Hospital,
Don Mariano Cui Street, Fuente Osmeña, Cebu City,
Cebu 6000 Philippines
Tel. No.: +63-032-255-8000
E-mail: anj0321ong@gmail.com
ORCiD: https://orcid.org/0000-0001-6671-0636

the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV).[14-16]

The cure for COVID-19 remains elusive. Continual shifts in the therapeutic recommendations occur as clinical trials evaluate the effectiveness of potential agents. Investigators are looking into possible risks and added benefits of current antihyperglycemic medications to ascertain their impact on the course and prognosis of COVID-19 patients with diabetes.

Metformin is an established antidiabetic agent. Despite the introduction of new drugs in the treatment of type 2 diabetes mellitus, metformin is commonly used and is considered a mainstay treatment.[17] Aside from its glucose-lowering action, other potential underlying mechanisms explaining the favorable impact of metformin on the COVID-19 patients with diabetes have been explored, including its effect on reducing cytokine storm.[18,19]

A study by Cheng et al., supported the findings of a higher incidence of lactic acidosis in metformin users, especially with severe COVID-19 disease. Acidosis occurred in patients with higher (<3 g per day) metformin doses compared to when given lower (<1 g per day) or moderate (<2 g per day) doses of the drug.[20] However, metformin rarely causes lactic acidosis on its own. Clinical conditions associated with increased circulating lactate levels include hypoxia, sepsis, chronic kidney disease, or decreased renal function and heart failure.[21] Due to the risk of lactic acidosis with infections, clinicians discontinue metformin in most patients with severe illness, including COVID-19 infection.[22,23] Despite the risk, the degree of mortality was comparable between the metformin and non-metformin groups in COVID-19 infected patients,[20] which supports its continued use in COVID-19 patients with diabetes, despite physician reluctance.

Because metformin is a cornerstone of management in patients with type 2 diabetes mellitus due to its therapeutic effects on glucose control and low cost, it is important to determine the outcome with its use in COVID-19 patients.

METHODOLOGY

Our study was a cross-sectional analysis done in two tertiary hospitals in Cebu, Philippines. The study population included patients admitted and subsequently included in the COVID-19 database of Chong Hua Hospital – Fuente and Chong Hua Hospital – Mandaue from March 1, 2020, to September 30, 2020.

All hospitalized Filipino patients who tested positive for COVID-19 via RT-PCR, are 18 years or older, and have type 2 diabetes mellitus, either preexisting or newly diagnosed using the American Diabetes Association criteria, were included in the analysis. We excluded patients if they had type 1 diabetes mellitus, were pregnant, of a different race or ethnicity, had unknown final disposition and those who were transferred to another institution or discharged against medical advice.

We categorized patients as to use or non-use of metformin, subdividing the metformin group into home metformin users, in-hospital metformin users, and mixed home/in-hospital metformin users. We retrospectively reviewed the characteristics and medications of these patients using an electronic medical record system.

The primary outcome was in-hospital mortality defined by a recorded final disposition of either discharged improved or death. Survival function between both groups was also an additional outcome measured.

Sample size

In the study by Lalau et al.,[24] which included 2449 people with type 2 diabetes mellitus, mortality on day 28 was 16% among metformin users, and 28.6% among non-users. To show a similar difference in mortality, we estimated that the sample size would have to be at least 311 persons with type 2 diabetes mellitus, similar to the population of Lalau. The Chong Hua Hospital database of COVID-19 patients from March 2020 to September 2020 revealed 952 patients, 355 of which had type 2 diabetes mellitus. It is these persons with diabetes who were included in our present study.

Ethical considerations

The Chong Hua Hospital Institutional Ethics Review Committee approved the study. Confidentiality was ascertained using a coding system. The principal investigator was responsible for the accuracy and integrity of the data presented. Data collection was compiled and stored in a personal computer system and tabulated in Microsoft Excel format.

Data analysis

The independent variable was metformin use, whether home use, in-hospital use, or mixed home/in-hospital use. Also, assessed were potential confounding comorbidities and medications that may cause protection or harm for patients with COVID-19 infection.

Age and glycemic control using admission HbA1c were expressed in mean ± standard deviation. Categorical variables, namely sex, body mass index, preexisting medical conditions, preadmission and in-hospital medications, and disease severity, were expressed in percentages. Chi-square test of independence was used to compare variables between metformin users and non-users and between the three subgroups of metformin users. Univariate logistic regression analysis was done for these variables, computing for odds ratios for mortality.

Any significant variables were then included in the multivariate logistic regression model to adjust for any imbalance noted between study groups. The stepwise backward deletion was also done. We analyzed survival function using the Kaplan-Meier survival curve, and a log-rank test was run to determine if there were differences in the survival distributions between both groups. Stata BE version 17 was used. A p-value of less than 0.05 was considered significant.

RESULTS

Our hospital COVID-19 database observed 952 individuals admitted with COVID-19 between March 1, 2020, and September 30, 2020. Of these, 381 patients had type 2

diabetes mellitus, 26 were excluded (3 being non-Filipino, 22 being transferred or discharged against medical advice, and 1 with unknown disposition). Of the 355 persons with type 2 diabetes, 186 (52.4%) were metformin users, further categorized into home metformin users (n=109, 30.7%), in-hospital metformin users (n=40, 11.3%), and mixed home/in-hospital metformin users (n=37, 10.4%).

Tables 1A and 1B show the comparison of the demographic profile, clinical characteristics, and in-hospital use of anti-COVID medications of patients with type 2 diabetes mellitus hospitalized for COVID-19 who are metformin users versus non-users, and between the three subcategories of metformin users, respectively.

The total mean age of the population was 62.69 ± 12.21 years. The total population was composed of 198 (55.8%) males, 109 (58.6%) metformin users. Among the metformin users, 13.4% were overweight and 62.4% were obese, compared to 13% overweight and 65.1% obese in the non-metformin group. Age, sex, and body mass index between both groups were statistically similar.

Table 1A. Comparison of demographic profile, clinical characteristics, and in-hospital anti-covid medications among patients with type 2 diabetes mellitus hospitalized for COVID-19 infection who are metformin users versus metformin non-users

	Variable	Metformin users n=186	Metformin non-users n=169	*p*-value
Age (years)	Mean	61.61 ± 11.555	63.91 ± 12.837	0.174
	<45	14 (7.5%)	12 (7.1%)	
	45-55	40 (21.5%)	29 (17.2%)	
	56-65	62 (33.3%)	51 (30.2%)	
	66-75	52 (28%)	44 (26%)	
	76-85	13 (7%)	24 (14.2%)	
	>85	5 (2.7%)	9 (5.3%)	
Sex	Male	109 (58.6%)	89 (52.7%)	0.288
	Female	77 (41.4%)	80 (47.3%)	
Body Mass Index	Underweight (<18.5 kg/m^2)	4 (2.2%)	1 (0.6%)	0.763
	Normal (18.5-22.9 kg/m^2)	40 (21.5%)	35 (20.7%)	
	Overweight (23-24.9 kg/m^2)	25 (13.4%)	22 (13%)	
	Obese I (>25-29.9 kg/m^2)	64 (34.4%)	58 (34.3%)	
	Obese II (≥30 kg/m^2)	52 (28%)	52 (30.8%)	
Pre-existing Medical Conditions	Hypertension	136 (73.1%)	129 (76.3%)	0.460
	Bronchial asthma	13 (7%)	14 (8.3%)	0.773
	Acute coronary syndrome	4 (2.2%)	12 (7.1%)	0.044*
	Coronary artery disease	13 (7%)	21 (12.4%)	0.112
	Heart failure	2 (1.1%)	8 (4.7%)	0.076
	Chronic obstructive pulmonary disease	4 (2.2%)	2 (1.2%)	0.779
	Liver disease	8 (4.3%)	5 (3%)	0.711
	Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)	9 (4.8%)	37 (21.9%)	<0.001*
	Cerebrovascular disease	8 (4.3%)	9 (5.3%)	0.822
	Cancer	10 (5.4%)	9 (5.3%)	1.00
Preadmission injectable antihyperglycemic agent	Insulin	18 (9.7%)	34 (20.1%)	0.008*
	GLP-1 agonist	2 (1.1%)	1 (0.6%)	1.00
Preadmission oral antihyperglycemic agent	DPP-4 inhibitor	69 (37.1%)	52 (30.8%)	0.24
	Sulfonylurea	29 (15.6%)	21 (12.4%)	0.508
	Thiazolidinediones	2 (1.1%)	1 (0.6%)	1.00
	SGLT-2 inhibitors	19 (10.2%)	7 (4.1%)	0.05
	Glucosidase inhibitors	0	1 (0.6%)	0.957
Baseline severity of disease	Mild	32 (17.2%)	28 (16.6%)	0.460
	Moderate	81 (43.5%)	68 (40.2%)	
	Severe	35 (18.8%)	43 (25.4%)	
	Critical	16 (8.6%)	11 (6.5%)	
	Missing	0	1 (0.6%)	
Admission HbA1c		6.997 ± 2.351	7.590 ± 1.894	0.016*
In-hospital medications				
Tocilizumab		97 (52.2%)	88 (52.1%)	1.000
Antimalarials		14 (7.5%)	17 (10.1%)	0.492
Antivirals		120 (64.5%)	115 (68%)	0.543
Systemic steroids		109 (58.6%)	100 (59.2%)	0.904
Hemoperfusion		9 (4.8%)	11 (6.5%)	0.634
Convalescent plasma therapy (CPT)		8 (4.3%)	9 (5.3%)	0.822
Injectable antihyperglycemic agent	Insulin	47 (25.2%)	71 (42%)	0.001*
	GLP-1 agonist	1 (0.5%)	1 (0.6%)	1.000
Oral antihyperglycemic agent	DPP-4 inhibitor	64 (34.4%)	56 (33.1%)	0.861
	Sulfonylurea	10 (5.4%)	7 (4.1%)	0.785
	Thiazolidinediones	0	0	N/A
	SGLT-2 inhibitors	11 (5.9%)	4 (2.4%)	0.115
	Glucosidase inhibitors	0	0	N/A

Table 1B. Comparison of demographic profile, clinical characteristics, and in-hospital anti-COVID medications between the 3 subcategories of metformin users

Variable		Home Metformin Use n=109	In-hospital Metformin Use n=40	Mixed home/ in-hospital Use n=37	*p*-value
Age (years)	<45	6 (5.5.%)	5 (12.5%)	3 (8.1%)	0.256
	45-55	18 (16.5%)	13 (32.5%)	9 (24.3%)	
	56-65	38 (34.9%)	11 (27.5%)	13 (35.1%)	
	66-75	35 (32.1%)	7 (17.5%)	10 (27%)	
	76-85	10 (9.2%)	2 (5%)	1 (2.7%)	
	>85	2 (1.8%)	2 (5%)	1 (2.7%)	
Sex	Male	68 (62.4%)	26 (65%)	15 (40.5%)	0.098
	Female	41 (37.6%)	14 (35%)	22 (59.5%)	
Body Mass Index	Underweight (<18.5 kg/m^2)	2 (1.8%)	2 (5%)	0	0.685
	Normal (18.5-22.9 kg/m^2)	20 (18.3%)	9 (22.5%)	11 (29.7%)	
	Overweight (23-24.9 kg/m^2)	17 (15.6%)	4 (10%)	4 (10.8%)	
	Obese I (>25-29.9 kg/m^2)	39 (35.8%)	15 (37.5%)	10 (27%)	
	Obese II (≥30 kg/m^2)	30 (27.5%)	10 (25%)	12 (32.4%)	
Pre-existing Medical Conditions	Hypertension	84 (77.1%)	24 (60%)	28 (75.7%)	0.076
	Bronchial Asthma	9 (8.3%)	2 (5%)	2 (5.4%)	0.694
	Acute Coronary Syndrome	3 (2.8%)	1 (2.5%)	0	0.592
	Coronary Artery Disease	7 (6.4%)	5 (12.5%)	1 (2.7%)	0.235
	Heart Failure	2 (1.8%)	0	0	0.481
	Chronic obstructive pulmonary disease	1 (0.9%)	2 (5%)	1 (2.7%)	0.316
	Liver Disease	3 (2.8%)	3 (7.5%)	2 (5.4%)	0.440
	Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)	6 (5.5%)	3 (7.5%)	0	0.271
	Cerebrovascular Disease	6 (5.5%)	1 (2.5%)	1 (2.7%)	0.608
	Cancer	5 (4.6%)	3 (7.5%)	2 (5.4%)	0.802
Preadmission injectable antihyperglycemic agent	Insulin	14 (12.8%)	2 (5%)	2 (5.4%)	0.201
	GLP-1 agonist	1 (0.9%)	0	1 (2.7%)	0.509
Preadmission oral antihyperglycemic agent	DPP-4 inhibitor	50 (45.9%)	1 (2.5%)	18 (48.6%)	<0.001*
	Sulfonylurea	20 (18.3%)	3 (7.5%)	6 (16.2%)	0.249
	Thiazolidinediones	0	0	2 (5.4%)	0.019*
	SGLT-2 inhibitors	14 (12.8%)	0	5 (13.5%)	0.052
	Glucosidase inhibitors	0	0	0	N/A
Admission HbA1c		6.960 ± 1.914	7.071 ± 2.124	7.026 ± 1.560	0.951
In-hospital use of anti-COVID medications					
Tocilizumab		59 (54.1%)	19 (47.5%)	19 (51.4%)	0.680
Antimalarials		10 (9.2%)	2 (5%)	2 (5.4%)	0.569
Antivirals		70 (64.2%)	26 (65%)	24 (64.9%)	0.991
Systemic steroids		59 (54.1%)	28 (70%)	22 (59.5%)	0.293
Hemoperfusion		9 (8.3%)	0	0	0.033*
Convalescent plasma therapy (CPT)		8 (7.3%)	0	0	0.048*
Injectable antihyperglycemic agents	Insulin	27 (24.8%)	9 (22.5%)	11 (29.7%)	0.770
	GLP-1 agonist	0	0	1 (2.7%)	0.137
Oral antihyperglycemic agents	DPP-4 inhibitor	18 (16.5%)	21 (52.5%)	25 (67.6%)	<0.001*
	Sulfonylurea	4 (3.7%)	2 (5%)	4 (10.8%)	0.266
	Thiazolidinediones	0	0	0	N/A
	SGLT-2 inhibitors	2 (1.8%)	4 (10%)	5 (13.5%)	0.011*
	Glucosidase inhibitors	0	0	0	N/A

More patients suffered from acute coronary syndrome (p=0.044) and chronic kidney disease (p≤0.001) in the non-metformin group. More patients in the non-metformin group were on insulin therapy before admission (p=0.008).

Both groups were similar in other clinical profiles, including hypertension, bronchial asthma, coronary artery disease, heart failure, chronic obstructive pulmonary disease, liver disease, cerebrovascular disease, malignancy, and preadmission use of GLP-1 agonists and oral antihyperglycemic agents.

Among the three subgroups of metformin users, most patients with preadmission use of DPP4-inhibitors (p≤0.001) were on home metformin use, while patients on preadmission thiazolidinediones were in the mixed home/in-hospital metformin users (p=0.019). Other characteristics, clinical profile, and preadmission medications among the three subgroups were statistically similar.

Most metformin users (n=81, 43.5%) and metformin non-users (n=68, 40.2%) had moderate COVID-19 disease severity. There was no notable difference in the baseline severity of disease between both groups (p=0.460).

Better glycemic control was observed in patients taking metformin than non-users (p=0.016), while there was no difference in glycemic control between the three metformin groups (p= 0.951).

More metformin non-users required insulin therapy during hospitalization (p=0.001). Fewer patients on metformin at home were treated with DPP-4 inhibitors (p≤0.001) and SGLT-2 inhibitors (p=0.011) during hospitalization, but they required convalescent plasma therapy (p=0.048) and hemoperfusion (p=0.033) more frequently. The use of other in-hospital treatments, including tocilizumab, antivirals, antimalarials, and systemic steroids, were similar among the treatment groups. Among the antihyperglycemic agents, the use of GLP-1 agonists, sulfonylureas, and glucosidase inhibitors was identical between the three metformin subgroups.

In the metformin group, 33 (17.7%) died during hospitalization for COVID-19, compared to 57(33.7%) in the non-metformin group (p=0.001). More deaths occurred in those with critical COVID-19, with 31 (93.9%) deaths in the overall metformin group compared to 53 (93%) in the non-metformin group. No deaths were noted in patients with mild disease in the two groups.

Although more patients died among home metformin users (n=28, 84.8%), compared to both in-hospital (n=2, 6.1%) and mixed home/in-hospital users (n=3, 9.1%) (p=0.003), there was an overall low rate of mortality in overall metformin users compared to the metformin non-users.

Logistic regression analysis using each variable in a univariate fashion showed an increased odds ratio for mortality in patients with increased age (p≤0.001; OR=1.041), chronic kidney disease (p≤0.001; OR=3.248), and acute coronary syndrome (p≤0.001; OR=14.744).

Patients who were given tocilizumab (p=<0.001; OR=2.556), systemic steroids (p=0.048; OR=1.662), convalescent plasma therapy (p=0.042; OR=2.775), hemoperfusion (p=0.003; OR=3.960) and those started on in-hospital insulin therapy (p=0.010; OR=1.917) were also noted to have increased odds for mortality. The odds ratio for glycemic control using preadmission HbA1c and baseline severity of disease were not significant.

Metformin use was associated with lower odds for mortality (p=0.001; OR 0.424) compared to non-users. In-hospital metformin users (p=0.002; OR=0.103) and mixed home/in-hospital metformin users (p=0.005; OR=0.173) were also associated with lower odds for mortality compared to non-users.

Table 2 shows univariate logistic regression analysis using factors that may affect mortality and crude odds ratio for mortality between metformin users and non-users.

Metformin use, regardless of dosage from 500 mg to 2 g daily, was associated with a lower risk for mortality compared to patients not taking metformin (p=0.002). There was also a lower crude odds ratio for mortality among patients on ≥1 g to <2 g daily of metformin, compared to non-users and other dosages (p≤0.001; OR=0.252). However, analyzing metformin users only showed no association between metformin dosage and mortality noted (p=0.166) (Supplementary Table).

We did a multivariate logistic regression analysis on significant variables, namely: age, chronic kidney disease, acute coronary syndrome, tocilizumab, systemic steroid use, convalescent plasma therapy, hemoperfusion, in-hospital insulin use, and HbA1c. After controlling for these variables, metformin use was associated with reduced odds for mortality (p=0.01; OR=0.433). The stepwise deletion was also done in this model and still showed metformin use was associated with better mortality outcomes (p=0.008; OR= 0.430).

Table 3 shows multivariate logistic regression analysis for mortality controlled for significant confounders.

The survival distributions between metformin users and non-users were statistically different, showing the inequality of survival (χ2=5.67, p=0.017).

Figure 1 illustrates the Kaplan-Meier survival curve between metformin users versus non-users.

DISCUSSION

Findings from several studies demonstrate the negative impact of type 2 diabetes mellitus on the morbidity and mortality of COVID-19 infected patients.[10-13] Thus, the potential role of antihyperglycemic agents, especially metformin, in this viral infection should also be explored.

COVID-19 patients with diabetes have one or more accompanying comorbidities, higher levels of circulating inflammatory markers, worse lung involvement by chest imaging, and thus are associated with more severe disease, more complications, and higher mortality rate.[10-13] Poor glycemic control is associated with severe COVID-19 infection and increased mortality.[11,25]

Aside from its effects on glucose metabolism, another potential role of metformin is immunomodulation. It inhibits the mTOR pathway, which plays a role in viral protein production, viral replication and release, and is critical for apoptosis and senescence.[26] It can also cause modulation of the ACE2 receptor, which serves as the viral entry point via the AMP-activated protein kinase.[27,28] This medication provides anti-inflammatory effects, reducing the cytokine storm by decreasing TNFα and IL-6 levels and increasing IL-10.[18,19] A reduction in the neutrophil extracellular traps and neutrophil to lymphocyte count have also been observed.[29]

Patients with stage 3 to 5 chronic kidney disease or dialysis therapy were less likely to be on metformin therapy before and during admission. This was an expected finding since metformin is contraindicated in patients with end-stage renal disease, and those with an eGFR of less than 30 mL/min/1.73 m^2. Initiation of metformin therapy is also contraindicated in patients with eGFR of less than 45 mL/min/1.73 m^2.

Metformin has previously been reported to decrease the incidence of cardiovascular events in the landmark UK Protective Diabetes Study (UKPDS) which showed lower all-cause mortality and incidence of myocardial infarction with its use versus conventional treatment.[30] The SPREAD-DIMCAD study also showed a significantly lower cardiovascular endpoint for persons with type 2 diabetes with coronary artery disease in its metformin

Table 2. Univariate logistic regression analyses using factors that may affect mortality

Variable	Survivors (n=265)	Non-survivors (n=90)	Odds Ratio (95% CI)	*p*-value
Age	61.33 (12.20)	67.04 (1.81)	1.04137 (1.01961 - 1.06360)	<0.001*
Sex – Male	149 (56.23%)	49 (54.44%)	0.93043 (0.57538 - 1.50457)	0.769
Body Mass Index	27.81 (6.11)	27.49 (7.16)	0.99191 (0.95467 - 1.03062)	0.769
Hypertension	196 (74%)	69 (76.7%)	1.15671 (0.66056 - 2.02551)	0.611
Bronchial asthma	22 (8.3%)	5 (5.6%)	0.64973 (0.23855 - 1.76961)	0.399
Chronic obstructive pulmonary disease	5 (1.9%)	1 (1.1%)	0.58427 (0.06735 - 5.06873)	0.626
Liver disease	9 (3.4%)	4 (4.4%)	0.315 (0.033-2.986)	0.314
Chronic kidney disease (eGFR <60 ml/min/1.73 m^2)	24 (9.1%)	22 (2.4%)	3.24878 (1.71640 - 6.14922)	<0.001*
Heart failure	7 (2.6%)	3 (3.3%)	1.27094 (0.32161 - 5.02242)	0.732
Acute coronary syndrome	3 (1.1%)	13 (14.4%)	14.74458 (4.09613 - 53.07515)	<0.001*
Coronary artery disease	29 (10.9%)	5 (5.6%)	0.47870 (0.17950 - 1.27667)	0.141
Cerebrovascular disease	13 (4.9%)	4 (4.4%)	0.90161 (0.28632 - 2.83914)	0.860
Cancer	12 (4.5%)	7 (7.8%)	1.77811 (0.67773 - 4.66510)	0.242
Severity of disease (using mild as a comparator at baseline)				
Mild	49 (18.5%)	11 (12.2)		
Moderate	103 (39.9%)	46 (51.1%)	1.98941 (0.94864 - 4.172)	0.069
Severe	61 (23%)	17 (18.9%)	1.24143 (0.53247 - 2.89436)	0.617
Critical	23 (8.7%)	4 (4.4%)	0.77470 (0.22262 - 2.69588)	0.688
Missing	0	1 (1.1%)		
HBA1c	7.29987 (1.99)	7.17014 (2.55)	0.97148 (0.85608 - 1.10243)	0.654
Preadmission medications				
Insulin	36 (9.8%)	16 (17.8%)	1.37538 (0.72191 - 2.62035)	0.582
GLP-1 agonists	3 (1.1%)	0	0.000	1.000
Metformin	113 (42.97%)	30 (33.71)	0.67496 (0.40826 - 1.11590)	0.125
DPP-4 inhibitors	89 (33.58%)	32 (35.56%)	1.09105 (0.66092 - 1.80111)	0.733
Sulfonylureas	41 (15.5%)	9 (10%)	0.60705 (0.28250 - 1.30443)	0.201
Thiazolidinediones	2 (0.8%)	1 (1.1%)	1.47753 (0.13238 - 16.49124)	0.751
SGLT-2 inhibitors	23 (8.7%)	3 (3.3%)	0.36282 (0.10628 - 1.23858)	0.106
Glucosidase inhibitors	1 (0.4%)	0	0.000	0.999
In-hospital medications				
Tocilizumab	123 (46.42%)	62 (68.89%)	2.55633 (1.53909 - 4.24591)	<0.001*
Antimalarials	22 (8.3%)	9 (10%)	1.22727 (0.54309 - 2.77339)	0.622
Antivirals	176 (66.42%)	59 (65.56%)	0.96243 (0.58141 - 1.59313)	0.882
Systemic steroids	148 (55.85%)	61 (67.78%)	1.66286 (1.00434 - 2.75316)	0.048*
Convalescent plasma therapy	9 (3.4%)	8 (8.9%)	2.77506 (1.03704 - 7.42598)	0.042*
Hemoperfusion	9 (3.4%)	11 (12.2%)	3.96062 (1.58417 - 9.90206)	0.003*
Insulin	78 (29.43%)	40 (44.44%)	1.91795 (1.17193 - 3.13886)	0.010*
GLP-1 agonists	2 (0.8%)	0	0.132	1.000
Metformin	72 (27.1%)	5 (5.56%)	0.15768 (0.06149 - 0.40433)	<0.001*
DPP-4 inhibitors	93 (35.09%)	27 (30%)	0.79263 (0.47283 - 1.32872)	0.378
Sulfonylureas	14 (5.3%)	3 (3.3%)	0.61823 (0.17352 - 2.20266)	0.458
Thiazolidinediones	-	-	-	-
SGLT-2 inhibitors	15 (5.7%)	0	0.000	0.998
Glucosidase inhibitors	-	-	-	-
Crude odds ratio for mortality between metformin users versus non-users, with non-users as the reference group				
Metformin use	153 (57.7%)	33 (36.7%)	0.42438 (0.25881-0.69397)	0.001*
Crude odds ratio for mortality between 3 subgroups of metformin users, with non-users as the reference group				
Metformin use				
Home	81 (30.6%)	28 (31.3%)	0.67922 (0.39777-1.15984)	0.157
In-hospital	38 (14.3%)	2 (2.2%)	0.10341 (0.02408-0.44407)	0.002*
Mixed Home/In-hospital	34 (12.8%)	3 (3.3%)	0.17337 (0.05104-0.58888)	0.005*
Crude odds ratio between different metformin dosages, with metformin non-use as reference group				
Metformin dosage (mg/day)				
500 - <1000 (n=85)	66 (24.9%)	19 (21.1%)	0.56565 (0.30990-1.03247)	0.063
≥1000 - <2000 (n=79)	70 (26.4%)	9 (10%)	0.25263 (0.11769-0.54225)	<0.001*
≥2000 (n=19)	15 (5.7%)	4 (4.4%)	0.52397 (0.16622-1.65169)	0.27

group compared to its glipizide group.[31] This may explain the higher prevalence of acute coronary syndrome in patients admitted without prior metformin use in our study population.

After computing for crude odds ratio, our study showed that metformin use was associated with a lower risk for mortality compared to the non-metformin group. More patients in the non-metformin group in our study population had chronic kidney disease and acute coronary syndrome, which can also be associated risk factors for mortality.

Tocilizumab, systemic steroids, hemoperfusion, convalescent plasma therapy, and in-hospital insulin use were also associated with mortality. The association noted between mortality and the use of these medications, especially tocilizumab, may be because of more severe diseases requiring these treatments.

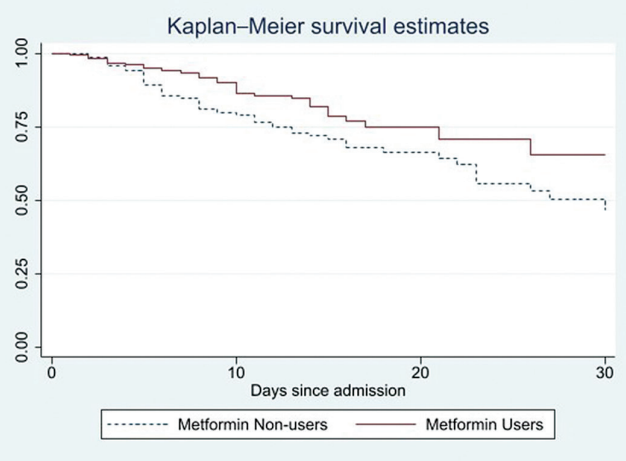

Figure 1. Kaplan-Meier survival curve between metformin users versus non-users.

Table 3. Multivariate logistic regression analyses for mortality controlled for significant confounders

Variable	Odds Ratio (95% CI)	*p*-value
Metformin use	0.43320 (0.22869-0.82061)	0.010*
Age	1.02510 (0.99773-1.05322)	0.073
Chronic kidney disease	2.08117 (0.78501-5.51749)	0.141
Acute coronary syndrome	14.80458 (2.89512-75.70515)	0.001*
Tocilizumab	2.31083 (1.11154-4.80409)	0.025*
Systemic steroids	1.35679 (0.64987-2.83268)	0.417
Convalescent plasma therapy	2.07477 (0.62739-6.86119)	0.232
Hemoperfusion	3.56889 (1.03360-12.32302)	0.044*
In-hospital insulin use	1.25407 (0.63349-2.48259)	0.516
HbA1c	0.96426 (0.82677-1.12461)	0.643
Using stepwise deletion		
Metformin use	0.43064 (0.23006-0.80609)	0.008*
Age	1.02656 (0.99984-1.05399)	0.051
Chronic kidney disease	2.18395 (0.84120-5.67001)	0.109
Acute coronary syndrome	15.36630 (3.00181-78.66032)	0.001*
Tocilizumab	2.65869 (1.35206-5.228065)	0.005*
Hemoperfusion	3.72632 (1.07222-12.9502)	0.038*
Convalescent plasma therapy	2.14171 (0.65775-6.97367)	0.206

After adjusting for these significant variables using multivariate logistics regression, metformin use, whether in the hospital or mixed home/in-hospital use, was still associated with a lower risk for mortality. This correlates with studies by Bramante[32] and Luo[33] who showed mortality benefits in patients with preadmission and in-hospital metformin use, respectively. Three other studies similarly showed the beneficial effects on overall mortality by this medication.[24,34,35] The CORONADO study also noted a lower risk for death in patients on metformin therapy.[36,37]

Our study finding, however, differed only from the study by Cheng et al., which concluded there was no difference in outcomes of patients with and without metformin use.[20] Our study showed a metformin dose from 500 mg to 2000 mg per day was associated with a lower risk for mortality. The greatest benefit was seen with a dosage between 1000 mg to <2000 mg daily. Patients taking higher metformin doses had fewer deaths, but estimates of benefit across dose categories cannot be made due to the small study population. No reports have currently surfaced recommending an optimal protective dose of metformin, and prospective studies are suggested or ongoing.

Luo et al. found no significant difference in the length of hospital stay between both groups.[33] The CORONADO study noted lower death rates at day seven and higher chances of discharge among patients on metformin therapy.[36-37] The study done by Lalau[24] showed lower mortality rates for metformin users on day seven and day 28. Our study showed that metformin users were associated with longer survival than non-users.

Results of this retrospective observational study showed beneficial effects of metformin on mortality in patients with type 2 diabetes mellitus hospitalized for COVID-19. Randomized controlled trials are still ongoing, and their results may or may not be similar to our study findings.

CONCLUSION

Metformin was associated with a lower risk for mortality in patients with type 2 diabetes mellitus hospitalized for COVID-19 disease, especially in patients with in-hospital and mixed home/in-hospital metformin use. Metformin, regardless of dosage, was associated with a lower risk for mortality compared to its non-use. The greatest benefit was seen in those on a daily dose of ≥1000 mg to <2000 mg. Despite the results from this study, the decision whether to initiate metformin in patients hospitalized for COVID-19 infection is upon the physician's discretion.

Limitation and Recommendation

Most patients in our study population had moderate disease. Therefore, our study results may not apply to patients with severe or critical COVID-19 infection.

We only collected data from admitted Filipinos with type 2 diabetes, and results may differ in the outpatient setting and among different ethnicities or races. The duration of metformin intake is not specified in this study. Compliance with preadmission metformin was also lacking and could not be assured. Several cells had frequencies less than 5, and significance may not be valid. Mortality prediction scoring, such as APACHE II and qSOFA, was not applied to help determine baseline risk for death between metformin users and non-users. Other confounding variables such as comorbid conditions and medications not included in this study analysis may also affect study results.

Findings were obtained from a retrospective observational study, and due to limitations, any results derived should be considered only hypothesis-generating. We recommend prospective studies to ensure complete data, fewer potential biases, and confounders.

A randomized prospective study can best determine the definitive effect of metformin on mortality in COVID-19 disease. Further sub-analysis on the beneficial effects of metformin on mortality outcome and survival time between different disease severities may also be investigated with a bigger study population.

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APPENDIX

Supplementary Table 1. Association between metformin dosage and mortality

Metformin users with dosage from 500 mg to 2000 mg daily versus no metformin use					
Metformin dosage (mg/d)			**Mortality**		***p*-value**
0			57		0.002*
500-<1000			19		
≥1000-<2000			9		
≥2000			4		
Dosage from 500 mg to 2000 mg daily among metformin users					
Metformin dosage (mg/d)		**Alive**	**Mortality**		***p*-value**
500-<1000		66	19 (22.4%)		0.166
≥1000-<2000		70	9 (11.4%)		
≥2000		15	4 (21.1%)		
Dosage from 500 mg to 2000 mg daily among three subcategories of metformin users					
Metformin dosage (mg/d)	**Home metformin use n=109**	**In-hospital metformin use n=40**	**Mixed home/in-hospital use n=37**	**Mortality**	***p*-value**
500-<1000 n=85	56	15	14	19 (22.4%)	0.166
≥1000-<2000 n=79	36	23	20	9 (11.4%)	
≥2000 n=19	14	2	3	4 (21.1%)