The Length of Hospital Stay in COVID-19 Patients Using Pre-hospital Metformin at a Saudi Tertiary Hospital: A Retrospective Cohort Study

Authors and affiliations

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Abstract

Background

Type 2 diabetes mellitus (T2DM) is prevalent in Saudi Arabia and is associated with severe outcomes from Coronavirus Disease 2019 (COVID-19). Metformin, the most prescribed medication for T2DM, has shown potential antiviral and anti-inflammatory properties that may be relevant in patients with COVID-19. This study evaluated the association of pre-hospital metformin use with length of hospital stay and secondary outcomes among patients with COVID-19 and T2DM.

Methods

This retrospective cohort study was conducted at King Abdulaziz Medical City in Jeddah from 2020 to 2023 and included hospitalized adult patients with confirmed COVID-19 and pre-existing T2DM. Pre-hospital metformin use was defined as documented within 90 days before hospital admission. Clinical characteristics, treatments, and hospital outcomes were analyzed using electronic health record data.

Results

Metformin use was associated with a significantly shorter hospital stay, with a median time to discharge of five days (95% CI: 4-6) compared with 14 days (95% CI: 7-44) in the non-metformin group. Metformin use was associated with a higher hazard of discharge than nonuse (HR = 1.85, 95% CI: 1.14–3.0; p = 0.012). No statistically significant differences were observed between the two groups for secondary outcomes, including mechanical ventilation, intensive care unit admission, and respiratory complications, defined as acute respiratory distress syndrome and severe respiratory failure.

Conclusion

Among hospitalized patients with type 2 diabetes and COVID-19, metformin use was associated with shorter hospital stays and a higher discharge rate. However, given the retrospective, single-center design, potential survivor bias, and residual confounding, these findings should be interpreted cautiously. Prospective multicenter studies using competing-risk approaches and incorporating mortality outcomes are recommended.

Keywords: COVID-19, Type 2 diabetes mellitus, Metformin, Hospital stay

Background

Coronavirus disease 2019 (COVID-19) is caused by the highly transmissible severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although it primarily targets the respiratory system, it can also involve multiple extrapulmonary organs, including the renal and cardiovascular systems [1]. Consequently, the clinical manifestations and severity of COVID-19 are heterogeneous, reflecting the combined influence of viral factors and host-related risk profiles, with important implications for disease burden and outcomes at the population level [2]. According to the World Health Organization (WHO), over 800,000 confirmed cases and 9,000 deaths have been reported in Saudi Arabia [3]. Notably, numerous risk factors have been linked to the development of severe infection, including type 2 diabetes mellitus (T2DM), which is one of the most prevalent and clinically significant [4,5]. Approximately one-fifth of the adult population in Saudi Arabia is affected by T2DM [6].

The condition contributes to systemic dysfunction through multiple pathophysiological mechanisms, including chronic low-grade inflammation characterized by elevated levels of proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α), which have been implicated in the increased morbidity and poor outcomes observed in patients with COVID-19 [4]. Furthermore, individuals with type 2 diabetes mellitus (T2DM) often exhibit a dysfunctional immune response, making them more susceptible to infections such as COVID-19 [7].

Diabetes is a systemic disease that affects multiple organs, including the eyes, nerves, kidneys, heart, and blood vessels [8]. The most common complication of T2DM is diabetic nephropathy, the leading cause of end-stage renal disease (ESRD) worldwide [9]. Diabetic nephropathy is a chronic microvascular complication of prolonged hyperglycemia, characterized by progressive structural and functional renal changes, including mesangial expansion, podocyte injury, and glomerulosclerosis. These changes can lead to a gradual decline in glomerular filtration rate and, if untreated, progress to ESRD [10].

Atherosclerotic cardiovascular disease (ASCVD), the leading cause of death in patients with diabetes, is associated with increased risk because diabetes itself is a significant independent risk factor. Greater glycemic variability has been linked to a higher risk of major adverse cardiovascular events, including increased cardiac mortality and heart failure. This association indicates that not only chronic hyperglycemia but also fluctuations in blood glucose contribute to the development and progression of ASCVD [11]. In addition, dyslipidemia, an important risk factor for ASCVD, is more common in patients with diabetes [12]. Patients with type 2 diabetes mellitus (T2DM) have increased susceptibility to infections, including COVID-19, due to impaired immunity and chronic inflammation, which are associated with a higher risk of severe outcomes such as intensive care unit admission and mortality [13].

Metformin, the most prescribed medication for T2DM, is a biguanide that enhances glucose uptake and suppresses hepatic gluconeogenesis. Beyond its metabolic effects, metformin is of particular interest in patients with diabetic COVID-19 because it has been shown to be beneficial due to its potential antiviral and anti-inflammatory properties. Several studies conducted in humans and cell-culture models have demonstrated that metformin inhibits SARS-CoV-2 growth and replication while reducing the levels of the pro-inflammatory cytokines IL-6 and TNF-α [14–16].

In the literature, numerous studies have investigated the association between metformin and COVID-19 in patients with T2DM. A study reported that T2DM patients receiving metformin had a lower in-hospital mortality rate and a reduced need for invasive mechanical ventilation compared with those not treated with metformin [5]. Another retrospective analysis demonstrated a significant reduction in mortality among women taking metformin [4]. Furthermore, a meta-analysis of 19 studies conducted by Li et al. [17] revealed that metformin use was associated with a 34% decrease in COVID-19-related mortality and 27% reduction in hospitalization rate.

Long after the COVID-19 pandemic, multiple studies continue to investigate the potential relation between metformin use and COVID-19 outcomes, and are still emerging in the literature, given the compelling evidence supporting their positive correlation [18–21]. This fact underscores the need to further examine this connection. According to the available literature, significant knowledge gaps persist regarding the effectiveness of metformin in the prognosis of COVID-19 diabetic patients in Saudi Arabia. To the best of our knowledge, no published primary studies have specifically evaluated metformin's effectiveness in the Saudi population. Although international observational studies and meta-analyses have examined the association between metformin use and COVID-19 outcomes, there remains a paucity of large-scale, methodologically robust, Saudi-specific studies directly evaluating this relationship, thereby limiting the generalizability of global findings to the local context [4,5,17].

Furthermore, the Saudi population is characterized by a high burden of obesity, metabolic syndrome, and multiple cardiometabolic comorbidities, which may alter pharmacodynamic and pharmacokinetic responses to metformin and potentially modify its therapeutic impact on COVID-19 outcomes [22]. Despite the existence of international evidence, the lack of comprehensive regional studies underscores the critical need for targeted investigations; therefore, conducting a population-specific study is necessary to accurately assess metformin effectiveness in Saudi patients and to ensure that clinical recommendations are evidence-based and locally applicable.

Given the high prevalence of diabetes in the Saudi population and emerging evidence of metformin's potential protective mechanisms, this research is particularly important. Accordingly, this study primarily aims to assess the association of metformin with the prognosis of COVID-19 patients admitted to a tertiary care center, including its impact on length of hospital stay, mechanical ventilation, intensive care unit (ICU) admissions, and respiratory complications.

Methods

Study design and setting

This retrospective cohort study was conducted at King Abdulaziz Medical City in Jeddah. All eligible patients who met the inclusion criteria were included, and data were collected from the BESTCare system covering the period from 2020 to 2023.

Eligibility criteria

We included all patients aged 18 years or older with a confirmed COVID-19 infection by polymerase chain reaction and a prior diagnosis of type 2 diabetes mellitus who were receiving antidiabetic medications at the time of infection. To be included in the metformin group, patients had to have documented metformin use for at least 90 days prior to hospital admission. This definition of metformin exposure aligns with prior observational studies examining metformin and COVID-19 outcomes to identify chronic use and minimize exposure misclassification [23]. Metformin dose and total therapy duration were recorded but not included as analytical variables; exposure was defined dichotomously as chronic use (≥90 days prior to admission). Eligible patients were also required to complete documentation of hospitalization outcomes. Each patient in the health system is assigned a unique medical record number, which allows identification of repeat hospitalizations; if a patient had multiple admissions during the study period, only the first index admission meeting inclusion criteria was included in the analysis. Exclusion criteria included patients with type 1 diabetes, acute heart failure, end-stage renal disease (ESRD), pregnancy, or those who died during hospitalization.

Data collection

Secondary data were collected for all patients who met the predefined eligibility criteria during the study period. The variables included clinical characteristics (age, gender, smoking status, height, and weight), presenting symptoms at admission (fever, chills, cough, chest pain, fatigue, rhinorrhea, sore throat, dyspnea, palpitations, diarrhea, nausea, vomiting, constipation, altered level of consciousness (LOC), body aches, dysuria, abdominal pain, diaphoresis, loss of taste and smell, dizziness, decreased oral intake, and headache), and medication history, including calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEi), beta-blockers, angiotensin receptor blockers (ARBs), diuretics, insulin, dipeptidyl peptidase 4 inhibitors (DPP-4i), thiazolidinediones (TZDs), sodium-glucose cotransporter-2 inhibitors (SGLT2i), sulfonylureas, glucagon-like peptide-1 agonists (GLP-1 agonists), and alpha-glucosidase inhibitors. Temporal (pandemic-era) effects, vaccination status, and specific COVID-19 treatment protocols were not included as covariates due to inconsistent availability in the electronic health record across the study period. Comorbidities were also collected including asthma, obstructive sleep apnea, bronchiectasis, dyslipidemia, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), hypertension, heart failure, chronic kidney disease (CKD stage 4 or less), ischemic heart disease (IHD), and cerebrovascular disease. Additionally, hospital course variables were recorded, including admission and discharge dates, mechanical ventilation, ICU admission, acute cardiac events, severe respiratory failure,ARDS, and secondary infection. Metformin use was documented for at least 90 days prior to hospital admission. For patients receiving metformin, the dosage (mg) and duration of therapy were also collected. Medication data were obtained from the admission Best Possible Medication History, which is routinely performed for all patients and verified by a clinical pharmacist within 24 hours according to a standardized institutional medication reconciliation protocol (APP 1443-15).

In addition to ILD and bronchiectasis, certain symptoms, specifically constipation, diaphoresis, headache, body aches, abdominal pain, loss of smell and taste, and dizziness, were excluded from the analysis because each was reported in only a single case in either the metformin or non-metformin group.

Post-mortem care and transfer protocols

Clinical death and postmortem transfers were managed in strict accordance with standardized institutional policies and regulatory requirements. Death was formally declared by the attending physician through electronic documentation, with mandatory reporting to the Ministry of Health completed within the required three hours. Internal transfers were performed exclusively using discreet transfer trolleys. Strict protocols were adhered to throughout each phase of the transfer process to ensure proper handling. For patients with COVID-19, infectious disease control protocols were implemented. These included the placement of the deceased in sealed, biohazard-labeled body bags and the mandatory use of full personal protective equipment by all personnel involved in handling and transfer procedures, ensuring the safety of staff and the broader healthcare environment.

Statistical analysis

Descriptive analyses were performed to summarize the data. Categorical variables were reported as frequencies and percentages. The Shapiro–Wilk test was used to assess the normality of continuous variables. Between-group comparisons were conducted using the Mann–Whitney U test or independent samples t-test for continuous variables and the chi-square or Fisher’s exact test for categorical variables, as appropriate. A Cox proportional hazards regression model was used to estimate the association between metformin use and time from hospital admission to discharge, adjusting for age, sex, hypertension, COPD, and baseline diabetes medications, including insulin and sulfonylurea use. Adjusted hazard ratio (HR) with 95% confidence intervals (CIs) was reported. A two-sided p-value < 0.05 was considered statistically significant. Survival analysis was performed to compare the time to discharge between patients with and without metformin use. All analyses were conducted using JMP® Pro (Version 17, SAS Institute Inc., Cary, NC).

Results

The clinical characteristics and baseline demographics of COVID-19 patients with type 2 diabetes mellitus are classified as metformin users or non-metformin users, are described in Table 1. The cohort consists of 114 patients, of whom 82 were in the metformin group, and 32 were in the non-metformin group. No statistically significant differences were observed between the groups in terms of age ($p = 0.13$), BMI ($p = 0.19$), or smoking status ($p = 0.99$). Similarly, the comorbidities, including asthma, obstructive sleep apnea, dyslipidemia, COPD, hypertension, heart failure, CKD≤ stage 4, ischemic heart disease, and cerebrovascular disease, did not differ significantly between the two groups (all $p > 0.05$).

At admission, symptoms included fever, chills, cough, chest pain, fatigue, rhinorrhea, sore throat, dyspnea, palpitations, diarrhea, nausea, vomiting, altered LOC, and dysuria. These symptoms were reported with comparable frequencies in both groups, with no statistically significant differences. A statistically significant difference was observed only for decreased oral intake, which was more prevalent in the non-metformin group (15.6% vs. 2.4%, $p = 0.018$).

Home medication use among the study population is summarized in Table 2. The distribution of most cardiovascular and antidiabetic medications, including calcium channel blockers, ACE inhibitors, beta-blockers, ARBs, diuretics, insulin, DPP-4 inhibitors, TZDs, SGLT2 inhibitors, and GLP-1 receptor agonists, was similar between the metformin and non-metformin groups. Insulin use was common (62.3%) and did not differ significantly between groups. In contrast, sulfonylurea use was significantly more frequent in the metformin group compared with the non-metformin group (26.8% vs. 9.4%, p = 0.047).

Table 2. Home medications in T2DM Patients Between the Metformin and Non-Metformin Groups.

Medication	Total (n=114)	Non-metformin (n=32)	Metformin (n=82)	P-value
CCB	50 (43.9)	17 (53.1)	33 (40.2)	0.21
ACEi	43 (37.7)	14 (43.8)	29 (35.4)	0.40
B-Blocker	44 (38.6)	10 (31.3)	34 (41.5)	0.31
ARBs	36 (31.6)	8 (25.0)	28 (34.1)	0.34
Diuretics	31 (27.2)	8 (25.0)	23 (28.0)	0.74
Insulin	71 (62.3)	23 (71.9)	48 (58.5)	0.18
DPP-4i	28 (24.6)	5 (15.6)	23 (28.0)	0.17
TZDs	3 (2.6)	2 (6.3)	1 (1.2)	0.18
SGLT2i	21 (18.4)	5 (15.6)	16 (19.5)	0.23
Sulfonylureas	25 (21.9)	3 (9.4)	22 (26.8)	0.047
GLP-1 agonist	9 (7.9)	4 (12.5)	5 (6.1)	0.26

n (%) are reported. Abbreviations: CCB, Calcium Channel Blocker; ACEi, Angiotensin-converting Enzyme Inhibitors; ARBs, Angiotensin Receptor Blockers; DPP-4i, Dipeptidyl Peptidase 4 Inhibitors; TZDs, Thiazolidinediones; SGLT2i, Sodium-glucose Cotransporter-2 Inhibitors; GLP-1, agonist Glucagon-like Peptide-1 Agonists.

Primary and secondary outcomes are summarized in Table 3. Event rates for mechanical ventilation, ICU admission, acute cardiac events, severe respiratory failure, ARDS, and secondary infection were consistently lower in the metformin group compared with the non-metformin group; however, these differences did not reach statistical significance (all p-values > 0.05).

Table 3. Primary and Secondary Outcomes Between Individuals in the Metformin and the Non-Metformin Groups.

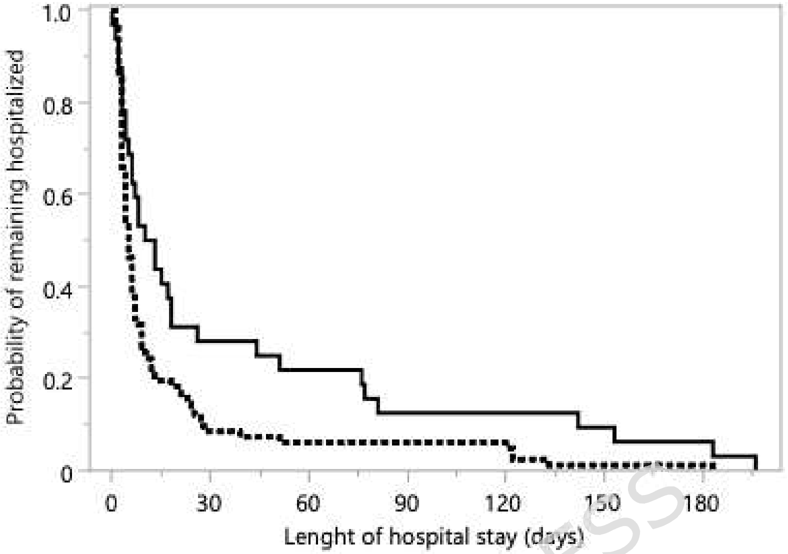
Outcome	**Total (n=114)**	**Non-metformin (n=32)**	**Metformin (n=82)**	**P-value**
Mechanical ventilation	17 (14.9)	7 (21.9)	10 (12.2)	0.19
ICU admission	20 (17.5)	6 (18.8)	14 (17.1)	0.83

Acute cardiac events	14 (12.3)	5 (15.6)	9 (11.0)	0.49
Severe respiratory failure	17 (14.9)	7 (21.9)	10 (12.2)	0.19
ARDS	16 (14.0)	6 (18.8)	10 (12.2)	0.36
Secondary infection	14 (12.3)	4 (12.5)	10 (12.2)	0.99

n (%) are reported. Abbreviations: ICU, Intensive Care Unit; ARDS, Acute Respiratory Distress Syndrome.

Survival analysis was conducted in **Figure 1** to evaluate the time from hospital admission to discharge in patients with and without metformin use. The median time to discharge was five days (95% CI: 4–6) in the metformin group, compared to 14 days (95% CI: 7–44) in the non-metformin group. Among metformin users, 25% were discharged by day 3 and 75% by day 11, whereas in the non-metformin group, 25% were discharged by day 6.5 and 75% by day 76.5. The wide confidence interval around the median and the high upper quartile in the non-metformin group reflect heterogeneity in length of hospital stay, with a small number of patients experiencing prolonged hospitalization. The log-rank test (Chi-square = 10.764, p = 0.001) and the Wilcoxon test (Chi-square = 10.64, p = 0.001) indicated a statistically significant difference in the time-to-discharge between groups. In the adjusted Cox proportional hazards regression model, metformin use was associated with a higher hazard of discharge compared with nonuse (HR =

1.85, 95% CI: 1.14–3.0; p = 0.012). The number-at-risk table illustrates patient distribution over time.



No. at risk

Days	0	30	60	90	120	150	180
Non-metformin	32	10	8	5	5	4	3
Metformin	82	8	6	6	5	2	2

Figure 1. Kaplan–Meier analysis of time to hospital discharge by metformin use. The y-axis represents the probability of remaining hospitalized. The table below the plot shows the number of patients at risk who had not yet been discharged at selected time points.

Discussion

This study shows that metformin use among patients with type 2 diabetes mellitus and COVID-19 was associated with a significantly shorter length of hospital stay and a higher likelihood of discharge. The median length of hospital stay was five days for metformin users compared with 14 days for non-users, representing a substantial association with an extension of previous research. Baseline demographic characteristics revealed no significant differences between the groups in age, BMI, or gender distribution, and both groups exhibited comparable burdens of pre-existing conditions, including hypertension and heart failure. This balanced distribution suggests that the metformin and non-metformin groups were comparable in terms of initial health status, thereby supporting the comparability of the two groups at baseline. One notable study reported that metformin was significantly associated with reduced mortality exclusively among women. This significant association in women compared with men might link to reduce TNFα to a greater extent in females than males in clinical and preclinical study [4].

Our results showed that metformin users had shorter hospital stays, as indicated by a higher hazard of discharge. These findings are consistent with previous evidence suggesting beneficial effects of metformin in patients with COVID-19. A territory-wide cohort study found that metformin users had approximately 2.76 days shorter hospital stays compared to non-users [23]. The larger effect size observed in our cohort may be attributable to differences in healthcare systems and patient demographics. Although the primary focus of this study was length of hospital stay, no significant differences were observed in secondary outcomes, including mechanical ventilation and ICU admission rates.

In our study, the initial analysis showed no significant difference in length of hospital stay between COVID-19 patients receiving metformin and those not receiving it. However, this finding was influenced by the inclusion of patients who died during hospitalization, as their prolonged hospital stay skewed the data. Consequently, these patients were excluded from the analysis to more accurately assess the impact of metformin on hospital stay length. Notably, prior evidence has indicated a possible benefit, with meta-analysis of 19 studies reporting associations between metformin use linked and reduced COVID-19 mortality (34%) as well as hospitalization rates (27%) [17].

The metformin group showed faster recovery, which may be attributed to the documented anti-inflammatory effects of metformin reported in several previous studies. In earlier studies, metformin users have demonstrated lower inflammatory markers, including TNF-α, IL-1β, IL-6, and various chemokines [24]. These anti-inflammatory effects, in turn, contribute to improving clinical outcomes such as a reduction in cardiovascular events

[25]. Additionally, the improved outcomes observed among metformin users may be partially associated with enhanced insulin sensitivity. By increasing insulin sensitivity, metformin promotes more stable glycemic control, which is particularly important for patients with diabetes who are at risk of severe COVID-19 [26].

The immunomodulatory effects of metformin may play an important role in the association of metformin among COVID-19 patients with diabetes. Metformin has been shown to suppress the activation of the NOD-like Receptor Family, Pyrin Domain-containing three inflammasome and diminishes the formation of neutrophil extracellular traps, both of which are key contributors to the pathophysiology of severe forms of COVID-19 and may thereby decrease the incidence of ARDS [27,28]. Furthermore, modulation of the immune response might help prevent the cytokine storm commonly observed in severe COVID-19 cases [29].

Metformin's primary action on mitochondria occurs through its inhibition of mitochondrial complex I, leading to suppression of mitochondrial reactive oxygen species signaling and reduction in oxidative stress within immune cells [30,31]. These effects are particularly relevant during viral infections such as COVID-19, where cellular stress and energy demands are increased, as they help support proper immune responses. These findings support the association of continuing metformin therapy in hospitalized COVID-19 patients with type 2 diabetes, provided no contraindications are present. This aligns with recent meta-analyses demonstrating that metformin use is associated with reduced mortality and disease severity among COVID-19 patients with diabetes [32]. Nevertheless, while this paper showed beneficial effects of metformin, it is important to note that previous research has identified a higher risk of acidosis in some COVID-19 patients on metformin particularly those with respiratory distress, heart failure, and renal impairment [23]. Therefore, careful monitoring of kidney function and acid-based status remains crucial in these patients.

Although the present study did not directly assess post-acute COVID-19 outcomes, emerging evidence suggests that metformin may influence the risk of post-COVID-19 conditions. Long COVID-19, also referred to as post-COVID-19 condition (PCC), usually occurs within three months of the initial COVID-19 illness and persists for at least two months, with a range of up to 200 different symptoms, including fatigue, aches, breathlessness, headaches, and difficulty in thinking or concentrating [33]. Recent evidence suggests that the established clinical criteria for Long COVID-19 may be insufficient and underestimate the full scope of the condition, as COVID-19 can cause significant end-organ damage in both symptomatic and asymptomatic individuals [34]. Furthermore, different autoimmune diseases have been reported as post-COVID-19 conditions, or long COVID-19, including systemic lupus erythematosus, myasthenia gravis, Graves' disease, and autoimmune hemolytic anemia [35]. All COVID-19 patients are at risk of developing PCC. However, patients with severe COVID-19 requiring hospitalization or ICU admission are at increased risk [33].

Therefore, due to its anti-inflammatory effects and possible role in faster recovery and hospital discharge, metformin might play a role in PCC prevention. A study shows that patients prescribed metformin within a week of confirmed COVID-19 infection had a 53% lower risk of developing long COVID or death over six months compared with those receiving comparator medications [36].

In this study, having only five patients who underwent computed tomography (CT) scan limited our ability to correlate clinical outcomes with radiological findings. Although CT scan can detect structural abnormalities associated with COVID-19, it does not directly capture impairment of gas exchange. In the study by Li et al. [37], it was demonstrated that post-COVID-19 patients with near-normal CT findings still exhibited abnormalities in Hyperpolarized xenon-129 Magnetic Resonance Imaging (^{129}Xe MRI), indicating persistent physiological dysfunction despite apparently improved structural imaging. In research settings, hyperpolarized ^{129}Xe has shown considerable promise; however, its clinical implementation remains limited due to the high cost of production equipment and incompatibility with standard clinical MRI scanners. Consequently, an alternative approach utilizing proton-hyperpolarized gases, which are more cost-effective and compatible with any clinical MRI without modifications, is promising for future clinical application [38]. Advances in Nuclear Magnetic Resonance hyperpolarization have enabled the development of proton-hyperpolarized gas contrast agents that allow rapid, non-invasive assessment of lung ventilation despite their short polarization lifetimes. In the context of COVID-19, future research should prioritize non-invasive and clinically scalable imaging methods to objectively evaluate pulmonary function, therapeutic response, and longitudinal recovery. These techniques may also facilitate improved characterization of pulmonary physiological changes associated with metabolic therapies, including metformin, during acute infection and post-acute sequelae [39,40].

The primary strength of this study lies in its focus on a specific regional population in Saudi Arabia, thereby addressing an important gap in the existing literature. The single-center design and focus on hospitalized patients may limit the generalizability. Moreover, the lack of significant differences in secondary outcomes may reflect limited sample size rather than the true absence of effect. A further limitation is that patients who died during hospitalization were excluded from the time-to-discharge analysis, as death represents a competing event that precludes discharge alive. While this exclusion was intended to avoid distorting the length-of-stay outcome, it may introduce survivor bias and limit the generalizability of the findings, particularly regarding mortality outcomes.

Although metformin dose and duration were recorded, a dose–response analysis was not performed. Exposure was analyzed dichotomously based on chronic use (≥90 days), which may not fully capture potential pharmacologic gradients of effect. Additionally, adjustments were not made for other chronic medications (e.g., statins, antiplatelets agents and anticoagulants), nor for in-hospital treatments, including corticosteroids and immunomodulators. These medications may influence COVID-19 severity and length of stay and therefore represent potential unmeasured confounders. Another limitation is that Hemoglobin A1c was not systematically collected across groups, limiting our ability to associate the improved outcomes with better glycemic control.

Moreover, this study spanned 2020 to 2023 and therefore included patients from multiple phases of the COVID-19 pandemic, including the pre-vaccination period and later waves associated with different viral variants. Vaccination status, temporal/variant-era effects, or specific in-hospital COVID-19 therapies (such as corticosteroids or antivirals) were not accounted for. Given the retrospective design and evolving clinical practices during the pandemic, these factors may represent unmeasured confounders that could have influenced patient outcomes.

Given the established relevance of mortality in COVID-19 and in the metformin literature, future studies employing a competing-risks framework should provide a more comprehensive assessment of the relationship between metformin exposure, recovery, and mortality.

Conclusion

Overall, among hospitalized patients with type 2 diabetes mellitus and COVID-19, metformin use was associated with a significantly shorter length of hospital stay and a higher rate of discharge compared with non-use. The median hospital stay was 5 days in metformin users versus 14 days in non-users, corresponding to a higher hazard of discharge compared to non-use. Given the comparable baseline demographic and clinical characteristics between groups, this association appears independent of major measured confounders. However, the exclusion of patients who died during hospitalization from the time-to-discharge analysis may have introduced survivor bias and limited the interpretability of the findings, particularly with respect to mortality. In addition, the retrospective single-center design, lack of adjustment for in-hospital therapies and vaccination status, absence of systematic HbA1c data, and potential residual confounding restrict the generalizability of the observed association. Future research should focus on adequately powered, prospective, multicenter studies that incorporate mortality and validated severity markers as primary or secondary endpoints and apply competing-risk analytical frameworks to better characterize the relationship between metformin exposure, discharge outcomes, and in-hospital death.

Abbreviations

T2DM	Type 2 Diabetes Mellitus
COVID-19	Coronavirus Disease 2019
ICU	Intensive Care Unit
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
IL-6	Interleukin 6
TNF-α	Tumor Necrosis Factor alpha
ESRD	End-stage renal disease
ASCVD	Atherosclerotic Cardiovascular Disease
LOC	Level of Consciousness
CCB	Calcium Channel Blockers
ACEi	Angiotensin-converting Enzyme Inhibitors
ARBs	Angiotensin Receptor Blockers
DPP-4i	Dipeptidyl Peptidase 4 Inhibitors
TZDs	Thiazolidinediones
SGLT2i	Sodium-glucose Cotransporter-2 Inhibitors
GLP-1 agonists	Glucagon-like Peptide-1 Agonists
COPD	Chronic Obstructive Pulmonary Disease

ILD	Interstitial Lung Disease
CKD	Chronic Kidney Disease
IHD	Ischemic Heart Disease
HR	Hazard Ratio
CI	Confidence Interval
P-value	Probability value
BMI	Body Mass Index
ARDS	Acute Respiratory Distress Syndrome
AMPK	AMP-activated Protein Kinase
ACE2	Angiotensin-Converting Enzyme 2
PCC	Post-COVID-19 Condition
CT	Computed Tomography
^{129}Xe MRI	Hyperpolarized xenon-129 Magnetic Resonance Imaging

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (approval number: IRB/0387/24). The confidentiality and anonymity of participants were completely preserved, and only the research team had access to the data.

Consent for publication

Not Applicable

Availability of data and materials

The datasets generated during the current study are not publicly available due to patient privacy restrictions but are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no competing interests.

Funding

This research received no specific grant from any funding agency.

Authors' contributions

All authors contributed equally to the conception and design of the study, data collection, analysis, and interpretation. All authors were involved in drafting and revising the manuscript, have read and approved the final version, and agree to be accountable for all aspects of the work.

Acknowledgements

Not applicable.

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Table 1 Baseline Demographics and Clinical Characteristics in COVID-19 Patients with T2D Stratified by Metformin.

	All	**Non-metformin**	**Metformin**	**P-value**
	n=114	*n = 32*	*n=82*	
Female	58 (50.9)	15 (46.9)	43 (52.4)	
Male	56 (49.1)	17 (53.1)	39 (47.6)	0.67
Age in years, mean (SD)	66.8 (13.8)	63.5 (15.1)	68.1 (13.2)	0.13
BMI, mean (SD), Kg/m^2	32.4 (11.4)	34.5 (10.2)	31.6 (11.8)	0.19
Smoker	11 (9.6)	3 (9.4)	8 (9.8)	0.99
Comorbidities on admission				
Asthma	15 (13.2)	4 (12.5)	11 (13.4)	0.98
Obstructive sleep apnea	10 (8.8)	3 (9.4)	7 (8.5)	0.99
Dyslipidemia	7 (6.1)	1 (3.1)	6 (7.3)	0.67
COPD	3 (2.6)	0 (0.0)	3 (3.7)	0.55
Hypertension	81 (71.1)	22 (68.8)	59 (72.0)	0.73

Heart failure	24 (21.1)	5 (15.6)	19 (23.2)	0.78
CKD≤stage4	18 (15.8)	5 (15.6)	13 (15.9)	0.97
Ischemic heart disease	30 (26.3)	6 (18.8)	24 (29.3)	0.25
cerebrovascular disease	28 (24.6)	8 (25.0)	20 (24.4)	0.94
Symptoms on admission				
Fever	85 (74.6)	23 (71.9)	62 (75.6)	0.16
Chills	3 (2.6)	2 (6.3)	1 (1.2)	0.18
Cough	94 (82.5)	26 (81.3)	68 (82.9)	0.83
Chest pain	27 (23.7)	7 (21.9)	20 (24.4)	0.77
Fatigue	24 (21.1)	9 (28.1)	15 (18.3)	0.24
Runny nose	14 (12.3)	4 (12.5)	10 (12.2)	0.99
Sore throat	22 (19.3)	9 (28.1)	13 (15.9)	0.13
Dyspnea	78 (68.4)	25 (78.1)	53 (64.6)	0.16
Palpitation	3 (2.6)	2 (6.3)	1 (1.2)	0.18
Diarrhea	11 (9.6)	1 (3.1)	10 (12.2)	0.17
Nausea	9 (8.2)	4 (12.9)	5 (6.3)	0.26

Vomiting	18 (15.8)	6 (18.8)	12 (14.6)	0.58
Altered level of consciousness	5 (4.4)	2 (6.3)	3 (3.7)	0.61
Dysuria	3 (2.6)	1 (3.1)	2 (2.4)	0.99
Decreased oral intake	7 (6.1)	5 (15.6)	2 (2.4)	0.018*

N (%) are reported. Data were n (%) or median (IQR). P values were calculated by Mann–Whitney U-test for non-normally distributed continuous variables and Fisher’s exact test or χ2 test for categorical variables. $P < 0.05$ was considered significant between metformin group vs non-metformin group. Abbreviations: (SD) Standard Deviation, COPD Chronic Obstructive Pulmonary Disease, CKD Chronic Kidney Disease.