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RESEARCH ARTICLE

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# Metformin use and its association with various outcomes in COVID-19 patients with diabetes mellitus: a retrospective cohort study in a tertiary care facility

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## ABSTRACT

**Background:** Evidence shows that diabetes raises the probability of contracting COVID-19 and associated complications. We hypothesize that metformin, being pleiotropic, may improve COVID-19 in diabetics.

**Methods:** A retrospective cohort study was conducted with 421 COVID-19 patients with diabetes, hospitalized between 1st April 2020 and 31st March 2022 in a tertiary-care hospital. Patients with metformin or its combination constituted the study cohort (SC; $n=221$), while other antidiabetics constituted the reference cohort (RC; $n=200$).

**Results:** SC and RC were matched for mean age ± SD (SC: 53.3 ± 5.7 vs. RC: 54.3 ± 8.2 years). The mean length of hospitalization (days) was significantly shorter in SC (9.0 ± 5.7) than in RC (12.7 ± 6) ($p<0.02$). Metformin use was associated with reduction in mortality risk (OR: 0.106, 95% CI = 0.039–0.287; $p<0.001$). Moreover, SC also improved levels of LDH (OR: 0.243, 95% CI = 0.104–0.566; $p<0.001$), CRP (OR: 0.281, 95% CI = 0.120–0.659; $p<0.004$), and D-dimer (OR: 0.220, 95% CI = 0.089–0.539; $p<0.001$) than RC. The calculated number needed to treat for metformin was 3.1.

**Conclusion:** Metformin users have a decrease in hospital stay and mortality rates and improvement in LDH, CRP, and D-dimer levels. Therefore, metformin might protect against mortality in COVID-19 with diabetes.

## KEY MESSAGES

- The study observed that COVID-19 patients with diabetes on metformin had lower CRP levels than those on other antidiabetics.
- The incidence and mortality risk were significantly found to be reduced in metformin users than in non-metformin users.
- Improvement in D-dimer, LDH, and CRP levels were also associated with reduced mortality risk in metformin users.
- The number needed to treat shows three patients would have to receive metformin to prevent one additional death in COVID-19 with diabetes.
- Therefore, metformin could be beneficial in COVID-19, in addition to its effect on diabetes.

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## 1. Introduction

Coronaviruses are a group of enveloped, single-stranded, positive-sense RNA viruses that cause various human pulmonary diseases [1]. As of December 2022, COVID-19 was responsible for more than 530,000 deaths in India [2, 3]. The virus primarily affects the lungs, and the respiratory symptoms could be mild or severe, with acute respiratory distress syndrome (ARDS) causing severe hypoxia [4]. Virus-infected lung epithelial cells release inflammatory cytokines such as IL-6 and IL-8 [5]. Inflammatory cells enter the lungs of COVID-19 patients suffering from severe disease [6, 7], leading to a life-threatening systemic inflammatory condition called a cytokine storm. These inflammatory cells constitute adaptive and innate immune cells, in which the latter immune cells, dominantly neutrophils, cause lung damage [8–10].

Diabetics infected with COVID-19 suffer a poorer prognosis and greater mortality than non-diabetics [11]. Extreme blood sugar fluctuations in diabetics and the resulting metabolic disruptions potentially weaken immunological competence and compromise lung function. Therefore, lung infections are widespread in diabetics [12]. Mortality from COVID-19 is higher among diabetics [13]. On the other hand, the Italian National Institutes of Health reported that 35.5% of COVID-19 patients developed diabetes [14]. On 28th March 2020, statistics from the US-CDC indicated that diabetes was the most common (10.9%) primary health issue among severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients [15].

Metformin, the most prescribed oral antidiabetic medication, is immunomodulatory, decreasing the generation of pro-inflammatory cytokines. Clinical investigation shows that metformin lowers mortality in diabetics suffering from COVID-19 [16]. Metformin's multifaceted ability to regulate glycemic levels and attenuate endothelial dysfunction, inhibition of viral entry and subsequent infection, and modification of immune and inflammatory responses during COVID-19 underscore its beneficial effects. Anti-hyperglycemic mechanisms of metformin: decreased hepatic glucose production and increased skeletal myocyte glucose uptake mediated by the adenosine monophosphate-activated protein kinase (AMPK) pathway not only reduces blood glucose but also provides anti-inflammatory action. Therefore, metformin may be hypothesized to decrease the morbidity and mortality of diabetics infected by COVID-19 [17]. In addition, Metformin restores euglycemia and general metabolic control, reduces body mass index and triglyceride levels, and lowers the risk for macrovascular complications in diabetes. Susceptibility to and outcomes of COVID-19 depend on the patient's cardiovascular status. Several clinical studies have demonstrated metformin's ability to lower cardiovascular events in diabetes *via* enhanced expression of the Angiotensin-Converting Enzyme 2 (ACE2) receptor [18–21]. ACE2 receptor binding is a crucial step for virus entry, but treatment options that increase ACE2 expression may attenuate COVID-19 complications [23]. In the Renin-Angiotensin-Aldosterone system (RAAS) pathway, ACE1 causes an increase in blood pressure, raising systemic and pulmonary hypertension [24]. ACE2 not only counterbalances the hypertensive stimulus of ACE1 but also activates anti-inflammatory pathways after tissue injury. Furthermore, the virus decreases the expression of ACE2 after binding to it, lowering ACE2 levels observed in many cardiac disorders and ARDS [25]. Therefore, treatments that enhance ACE2 expression (such as metformin therapy) would presumably counter COVID-19. Therefore, the aforementioned effects of metformin make it a feasible molecule to consider for repurposing against COVID-19, especially for those with diabetes. See Figure 1 for a detailed graphical presentation of the pleiotropic benefits of metformin in COVID-19 [22].

A retrospective study in China reported in-hospital mortality rate was 2.9% and 12.3% in the metformin and non-metformin groups ($p = 0.01$), respectively [26]. CORONADO observational research involving 2449 diabetic patients hospitalized for COVID-19 in 68 French hospitals found that metformin users had fewer diabetic complications than non-users [27]. Similarly, an observational study among hospitalized COVID-19 patients with diabetes from 53 French hospitals reported that metformin use was associated with a decreased risk of early death [28]. Another study on diabetic COVID-19 patients found that using metformin before COVID-19 diagnosis significantly reduced the possibility of death, implying a protective role in this high-risk group [29]. Therefore, the study aimed to comparatively evaluate the various outcomes (including in-hospital mortality) of SARS-CoV-2 infection in type 2 diabetes mellitus (T2DM) patients using metformin/other oral antidiabetic drugs.

## 2. Patients and methods

### 2.1. Study design

A retrospective cohort study was carried out at Kasturba Hospital (KH), a 2032-bed tertiary care teaching hospital in the Udupi district of Karnataka state, South India. The hospital has been recognized as a dedicated COVID-19 care centre in the district. The duration of the study was one year. Data were

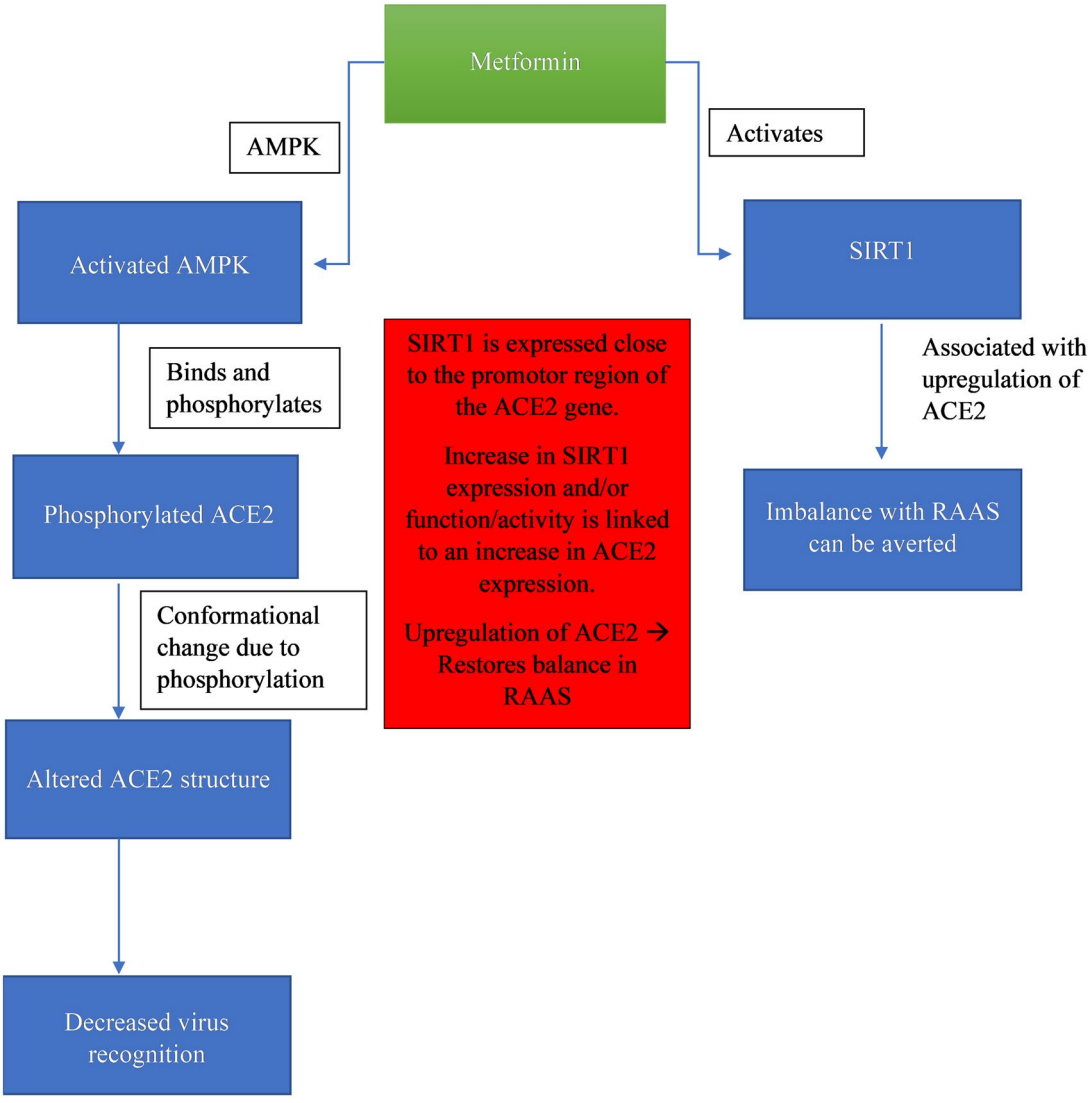


**Figure 1.** Mechanism of action of metformin in COVID-19.

collected from T2DM patients aged 18 years or older admitted to the hospital for COVID-19 infection between 1st April 2020 and 31st March 2022. Patients on metformin or its combination and other antidiabetic drugs were included in this study. Patients above 65 years, patients with type 1 diabetes (T1DM) and gestational diabetes, and those discharged against medical advice were excluded.

### 2.2. Ethical committee approval

Ethical approval was obtained from the Institutional Ethics Committee (IEC) of Kasturba Medical College and Kasturba Hospital (KMC&KH), Manipal (Reference No.: IEC: 662/2021, dated 25th February 2022). The study was registered in the Clinical Trial Registry of India (CTRI), Reg no: CTRI/2022/02/040064. Since it is a retrospective cohort study, the IEC has provided a waiver of informed consent to the participants. However, all the data were collected based on the rules of the Declaration of Helsinki of 1975, revised in 2013. In addition, we have followed the Indian Council of Medical Research's National Ethical Guidelines 2017 for biomedical and health research involving human participants.

### 2.3. Sample size calculation

The sample size of 124 per group was calculated assuming 0.05 alpha ($\alpha$) error, 80% power, 2.9% in-hospital mortality in the metformin group, and 12.3% rate in the reference group, based on the in-hospital mortality rates from a comparable study in a similar population [26]. On the other hand, to increase the statistical power, we increased the sample size from 248 to 421 patients, of which 221 were prescribed metformin and 200 with other antidiabetic medications.

### 2.4. Data collection

In-patient medical records were collected from the Medical Record Department (MRD) of Kasturba Hospital, Manipal, in accordance with inclusion and exclusion criteria (see Figure 2). All medical records of COVID-19 and T2DM patients admitted between 1st April 2020 and 31st March 2022 were retrieved using ICD-10 codes E11.0 to E11.9 and U07.1, respectively. Patient details were entered in the case record form (CRF). Demographical information (age and gender) was recorded along with COVID-19 symptoms on admission and severity. Details regarding antibiotics, antidiabetic drugs, supportive treatment, diabetic complications, duration of hospitalization, and biochemistry such as C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), glycosylated haemoglobin (HbA1c), random blood sugar (RBS) were also recorded.

### 2.5. Statistical analysis

Descriptive statistics were used to explain the characteristics of the study population. Quantitative variables were expressed as mean ± standard deviation (SD) for normally distributed data and median (interquartile range; IQR) for skewed data, and frequency and percentage for categorical variables. Paired *t*-test was used to compare the quantitative variables between the study and the reference cohorts. Binary logistic regression was applied to determine the association between various independent variables and the dependent variable, mortality. The results are expressed as odds ratio (OR), with $p < 0.05$ at 95% confidence interval. Statistical Package for the Social Sciences (SPSS)-version 28.0.1 was used to analyze the data.

## 3. Results

### 3.1. Characteristics of the study population

We selected 421 T2DM patients infected with COVID-19, of which 221 received metformin alone or its combination (study cohort; SC), and the remaining 200 received one or more antidiabetic medications other than metformin (reference cohort; RC). A detailed description of the study population is given in Table 1. Among the SC cohort, 291 (69.1%) were male, and 130 (30.8%) were female. Most SC patients had mild infections, whereas RC witnessed many patients with severe infections. Inflammatory markers such as CRP, D-dimer, and LDH were similar on the first day of admission in both cohorts. The mean (±SD) age of metformin users in the SC and RC were 53.3 ± 5.7 and 54.3 ± 8.2 years, respectively. The mean length of hospitalization ± SD was 9.0 ± 5.7 in SC as against 12.7 ± 6 in the RC, indicating significantly better outcomes among metformin users ($p < 0.02$).

### 3.2. Association of COVID-19 mortality with the different independent factors

Binary logistic regression was used to determine the association of the dependent variable (mortality) with different independent variables such as metformin use, dose, severity, HbA1c level; and improvement in LDH,

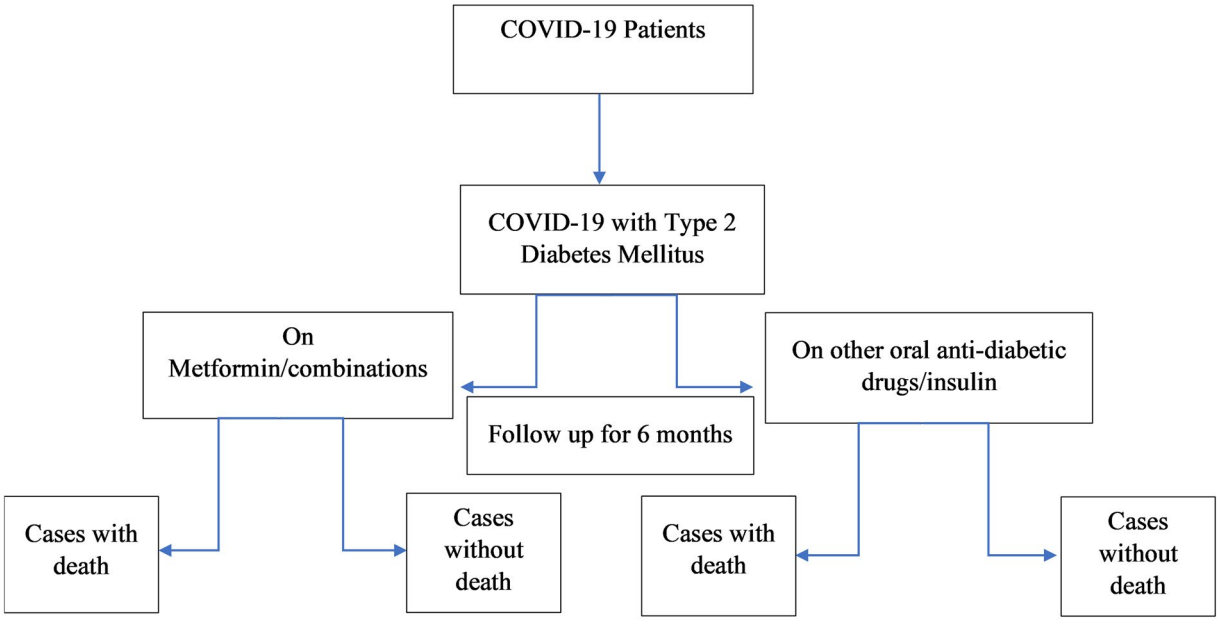


**Figure 2.** Study flow chart.

**Table 1.** Characteristics of the study population at baseline.

| Parameters | Study cohort ($n=221$) | Reference cohort ($n=200$) | $p$ value[#] |
|---|---|---|---|
| Age in years (mean ± SD) | 53.3 ± 5.7 | 54.3 ± 8.2 | 0.18 |
| Gender | | | – |
| • Male, *n* (%) | 148 (66.9 %) | 143(71.1%) | – |
| • Female, *n* (%) | 73 (33.1 %) | 57 (28.9 %) | |
| Duration of hospitalization in days (Mean ± SD) | 9.0 ± 5.7 | 12.7 ± 6 | 0.02* |
| Clinical severity | | | – |
| • Mild | 86 (38.9 %) | 34 (17 %) | |
| • Moderate | 72 (32.6 %) | 51 (25.5 %) | |
| • Severe | 63 (28.5 %) | 115 (57.5 %) | |
| Inflammatory markers (median with IQR) | | | – |
| • CRP in mg/L | 47.84 (93.84) | 85 (108.69) | |
| • D-dimer in ug/mL | 0.5 (1.25) | 1.1 (2.7) | |
| • LDH in U/L | 364 (262) | 452.5 (320) | |
| RBS in mg/dl (mean ± SD) | 236.7 ± 111.1 | 258.9 ± 133 | 0.10 |
| HbA1c in % (mean ± SD) | 8.68 ± 2.03 | 8.60 ± 2.30 | 0.70 |

[#]Paired *t* test;
*Statistically significant;
Abbreviations: SD: standard deviation; CRP: C – reactive protein; LDH: Lactate dehydrogenase; RBS: Random blood sugar; HbA1c: Glycosylated hemoglobin.

**Table 2.** Independent risk factors for mortality in COVID-19 patients with diabetes by univariate analysis.

| Variables | | Odds ratio | 95% CI | $p$ value[#] |
|---|---|---|---|---|
| Metformin use | | 0.740 | 0.03–0.16 | <0.001* |
| HbA1c | | 0.931 | 0.82–1.06 | 0.281 |
| Dose of Metformin | | 0.999 | 0.99–1.00 | 0.323 |
| Severity | Mild | 1 | – | – |
| | Moderate | 0.983 | 0.06–15.90 | 0.991 |
| | Severe | 84.000 | 11.46–615.22 | <0.001* |
| Improvement in Biomarkers | D dimer | 0.328 | 0.16–0.65 | 0.002* |
| | CRP | 0.189 | 0.11–0.34 | <0.001* |
| | LDH | 0.279 | 0.15–0.51 | <0.001* |

[#]Univariate binary logistic regression.
*Statistically significant.

**Table 3.** Independent risk factors for mortality in COVID-19 patients with diabetes by multivariate analysis.

| Variables | Adjusted odds ratio | 95% CI | $p$ value[#] |
|---|---|---|---|
| Metformin use | 0.106 | 0.04–0.29 | <0.001* |
| Improvement in D-dimer | 0.220 | 0.09–0.54 | 0.001* |
| Improvement in CRP | 0.281 | 0.12–0.66 | 0.004* |
| Improvement in LDH | 0.243 | 0.10–0.56 | 0.001* |

[#]Multivariate binary logistic regression.
*Statistically significant.

CRP, and D-dimer levels. Initially, all the variables were assessed individually through univariate analysis, which showed that except for metformin dose and HbA1c, the other variables (Metformin use, improvement in D-dimer, CRP, and LDH) were statistically significant (Table 2). After that, all the significant factors were screened using multivariate analysis until all the non-significant factors were eliminated. The results show that among metformin users, LDH, CRP, and D-dimer levels improved significantly, while the other factors lost their significance. Metformin use has shown a decrease in mortality risk by 0.106 times. Similarly, improvement in D-dimer, LDH, and CRP levels has shown a decrease in mortality risk by 0.220, 0.243, and 0.281 times, respectively, as depicted in Table 3.

### 3.3. Number needed to treat

The number needed to treat (NNT) is an epidemiologic metric used to assess the efficacy of a health-care intervention, most often a medication-based treatment. It is the average number of patients who need to be treated to avoid one additional undesirable outcome and is the inverse of the absolute risk reduction (ARR) when a study outcome is reported as a percentage.

In our study,
Total number of deaths in RC = 69,
Total number of patients in RC = 200,
Total number of deaths in SC = 7,
Total number of patients in SC = 221,
Therefore,

$$\begin{aligned}\text{ARR} &= \text{Control Event Rate}(\text{CER}) - \\ &\quad \text{Experiment Event Rate}(\text{EER}) \\ &= (69/200 - 7/221) = 34.5\% - 3.1\% = 31.4\%\end{aligned}$$

$$\text{NNT} = 1/\text{ARR} = 1/0.314 = 3.1 \approx 3$$

The calculated NNT was found to be 3.1.

## 4. Discussion

This study is the first to report the association of clinical outcomes, including mortality with metformin use in COVID-19 patients with T2DM in India. Many factors, including accessibility, cost, and reasonably acceptable safety profile, favor metformin use in clinical practice. Lower mortality was significantly associated with metformin use in COVID-19 with diabetes. Our findings were consistent with Ma et al. who found a protective association between metformin use and mortality in 1356 T2DM patients hospitalized with COVID-19 (OR: 0.25, 95% CI 0.06–0.74; $p=0.027$) [30]. Likewise, Crouse et al. study in the United States found that using metformin before the diagnosis of COVID-19 was associated with a three-time reduction in mortality than other antidiabetic medications [29].

Both mild and moderate severities were grouped during statistical analysis because there were no deaths in the mild severity group and only one in the moderate severity group. While 57.5% of non-metformin users developed severe symptoms, only 28.5% of metformin users developed severe symptoms, which was significantly lower.

The severity of COVID-19 was greater in patients with comorbidities, possibly because of higher ACE2

**Table 4.** Summary of the published studies on metformin therapy and mortality in COVID-19 patients.

| Sl. No | Author | Year | Country | Study design | Study population | Key findings |
|---|---|---|---|---|---|---|
| 1. | Luo, *et al.* [26] | 2020 | China | Retrospective Observational | 283 diabetic patients with COVID-19 were included, with 104 in the metformin group and 179 in the non-metformin group. | The in-hospital mortality was significantly lower in the metformin group ($n=3$; 2.9%) than in the non-metformin group ($n=22$; 12.3%) [$p = 0.01$]. |
| 2. | Lalau, *et al.* [27] | 2021 | France | Multicentred Retrospective cohort (CORONADO study) | 2449 diabetic patients hospitalized for COVID-19 in 68 French hospitals were selected, with 1496 patients in the metformin group and 953 patients in the non-metformin group. | The in-hospital mortality rate was lower in metformin users on day 7 (8.2 vs. 16.1%; $p<0.0001$) and day 28 (16.0 vs. 28.6%; $p<0.0001$). Metformin users were younger and had a reduced risk of diabetic complications than non-users, despite having more severe COVID-19 characteristics at the time of admission. |
| 3. | Cariou, *et al.* [28] | 2020 | France | Multicentred Retrospective Cohort (CORONADO study) | 1317 patients with diabetes who were hospitalized for COVID-19 were included. 746 of them took metformin, while the remaining 571 did not. | The risk of death on day 7 was lower in patients taking metformin (OR: 0.80, 95% CI: 0.45–1.43; p = 0.4532). |
| 4. | Crouce, *et al.* [29] | 2021 | USA | Retrospective Observational | 239 COVID-19 patients with diabetes were selected. 76 of them took metformin, while the remaining 163 did not. | The mortality rate in the metformin group ($n=8$; 19.1%) was significantly lower than that of the non-metformin group ($n=34$; 81.0%) [$p=0.0221$]. Furthermore, metformin treatment before diagnosis of COVID-19 was independently associated with a significant reduction in mortality (OR: 0.33, 95% CI = 0.13–0.84; $p=0.0210$). |
| 5. | Chen, *et al.* [37] | 2020 | China | Retrospective Observational | A total of 904 COVID-19 patients were selected, out of which 120 had diabetes. Within that, 43 patients took metformin, and the remaining 77 did not. | The in-hospital mortality of the metformin group ($n=4$; 9.30%) was lower than the non-metformin group ($n=15$; 19.48%) [$p=0.194$]. C-reactive protein may aid in identifying diabetic individuals who are at a higher risk of dying during hospitalization. |
| 6. | Bramante, *et al.* [38] | 2021 | USA | Retrospective cohort | The claims data of 6256 COVID-19 patients having diabetes was taken, out of which 3923 patients were in the metformin group and 2333 patients in the non-metformin group | The in-hospital mortality rate in the metformin group ($n=394$; 16.9%) was lower than that of the non-metformin group ($n=791$; 20.2%). Metformin was associated with decreased mortality in women by Cox proportional hazards (HR = 0·785, 95% CI = 0·650–0·951) and propensity matching (OR = 0·759, 95% CI = 0·601–0·960, $p=0·021$). However, there was no significant reduction in mortality among men (HR = 0·957, 95% CI = 0·82–1·14; $p=0·689$ by Cox proportional hazards). |
| 7 | Al-kuraishy, et al. [39] | 2023 | Iraq | Prospective cohort | A total of 100 patients were selected. 60 hospitalized T2DM patients with COVID-19 on metformin plus standard anti-COVID-19 treatments compared to 40 hospitalized T2DM patients with COVID-19 on other diabetic pharmacotherapy | The mortality rate in the metformin group was 5%, while the mortality rate in the non-metformin group was 22.5% ($p=0.0001$). Metformin treatment in T2DM patients with COVID-19 was more effective at lowering inflammatory and oxidative stress markers, leading to significant improvements in radiological scores and clinical outcomes. |

Abbreviations: OR: Odds ratio; HR: Hazard ratio; T2DM: Type 2 diabetes mellitus.

expression and lung inflammation, potentially leading to severe morbidity and mortality due to ARDS, multiple organ failure, and shock [31]. Underlying diseases, such as diabetes, have been identified as risk factors that increase the rate of mortality; therefore, correct assessment is essential during hospitalization. Several hypotheses have been proposed to explain the increased incidence of COVID-19 in diabetics. COVID-19 causes a powerful, long-lasting inflammatory "cytokine storm" linked to excessive inflammation in T2DM patients [32]. Therefore, repurposing an existing affordable, safe, efficacious drug candidate that simultaneously addresses both diabetes and COVID-19 presents a promising opportunity.

Our findings have shown that improvement in D-dimer levels is associated with a reduction in mortality, which is consistent with the reports of Poudel et al. [33, 34]. D-dimer measurement has significant diagnostic value in COVID-19 because thrombosis can occur in various organs with subsequent organ failure in severe COVID-19 cases. Another important finding was COVID-19 patients with higher LDH levels tended to be older and were more likely to require respiratory support. A study by Jin et al. found that LDH levels in severe COVID-19 were significantly higher than in non-severe cases and the healthy controls [35]. LDH levels in non-severe cases were also higher than in the healthy group. More patients with elevated LDH received anticoagulants and corticosteroids. Further research is needed to determine the effects of corticosteroids and anticoagulants on LDH in patients with COVID-19.

Finally, the NNT for metformin to prevent mortality was calculated to be 3.1, implying that, on average, three patients would have to receive metformin to prevent one additional COVID-19 death. While this favors metformin use among COVID-19 patients with diabetes, the United Kingdom Protective Diabetes Study (UKPDS) mandates metformin in the therapy for all T2DM patients if tolerated and not contraindicated because metformin is the only oral antidiabetic that reduces overall mortality risk [36]. In patients without severe renal impairment, metformin may be considered as a repurposed COVID-19 medication for all diabetic patients, regardless of current/possible pregnancy status. The summaries of the previous studies are shown in Table 4.

Our study has several limitations. The retrospective nature of the study introduces limitations such as unmeasured confounders and selection bias, limiting the ability to establish causal relationships between metformin use and clinical outcomes in COVID-19 patients with diabetes. Additionally, missing data, such as the duration of metformin use before COVID-19 infection, was not recorded, preventing us from evaluating the impact of long-term versus short-term metformin use on clinical outcomes. Missing data on vital clinical parameters, including body mass index (BMI), diabetes duration, and incomplete medication history, further weakens the robustness of our conclusions. Furthermore, we could not fully assess COVID-19 severity regarding clinical presentation, hypoxia status, and radiological findings, as these details were not consistently recorded for all patients. These limitations affect our findings' generalizability and the ability to draw definitive correlations between metformin use and COVID-19 prognosis.

Additionally, a significant limitation of this study is the relatively small sample size. The sample size was calculated based on in-hospital mortality rates from a comparable study in a similar population, which could have contributed to our analysis's smaller number of patients. This smaller sample size could reduce the statistical power and limit the generalizability of our findings. However, we noticed a significant association between single or short-term metformin exposure and a protective impact on COVID-19. In addition, metformin is generally used only in mild to moderate cases without hypoxia, hypotension, and renal insufficiency. Therefore, these factors are hindrances to the matching of both cohorts with different parameters. Moreover, we could not examine the effect of metformin on various biomarkers because the repeated values of the biomarkers were missing in the database.

## 5. Conclusion

Our study found that diabetics receiving metformin had lower CRP levels during admission than those on other antidiabetic drugs. This could be due to the anti-inflammatory properties of metformin. Also, the incidence and risk of mortality were significantly found reduced in the metformin users as compared to non-metformin users. Improvement in the levels of D-dimer, LDH, and CRP was also associated with a reduction in mortality risk. Most importantly, on average, three patients would have to receive metformin to prevent one additional death in diabetics with COVID-19. Therefore, Metformin could be co-prescribed in diabetics with COVID-19 if tolerated and not contraindicated.

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## Author contributions

M.S., S.K.M., S.J.K., and S.S.M. conceptualized the study. M.S., and S.K.M. collected the data. S.P., S.J.K., S.S.M., and V.K. cured the data. S.P., and V.K. analyzed the data. M.S., S.K.M, and S.S.M., wrote the manuscript. V.K., S.K., S.S., C.U.K., M.K.M., M.K.U., K.S., M.R., and S.S.M. critically evaluated the manuscript. All the authors participated in the manuscript review and approved the final draft of the manuscript.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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## Data availability statement

The dataset used or analyzed during the current study is available from the corresponding author upon reasonable request.

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Papers of special note have been highlighted as: * of interest ** of considerable interest.

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