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Research article

Effects of pre-existing metformin therapy on platelet count, serum creatinine, and hospitalization in COVID-19 patients with diabetes mellitus

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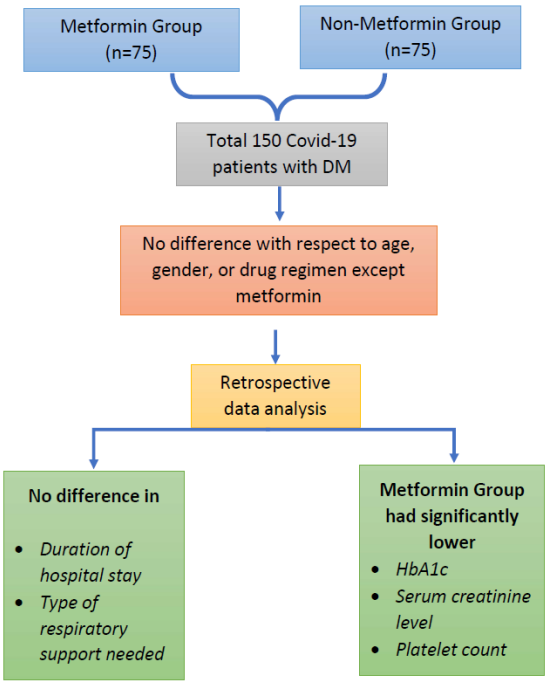
Abstract: COVID-19 infected individuals with type 2 diabetes mellitus are at higher risk of COVID-19 related complications. Previous studies have yielded varying results regarding the effect of metformin, an antidiabetic drug, on the clinical outcomes of COVID-19 patients. In this retrospective observational study, we aim to assess the impact of pre-existing oral antidiabetic treatment on the clinical outcomes of COVID-19.

We analyzed in-patient data from hospital records, enrolling 150 COVID-19 patients with pre-existing diabetes mellitus. Among them, 75 were treated with metformin, while the remaining 75 were not. Exclusion criteria included patients with type I diabetes mellitus and those above 85 years of age. Fisher's exact test, Chi square test and unpaired t-test were used to analyze the data. There were no significant differences between the two groups in terms of age, gender, or drugs prescribed, aside from metformin. However, the metformin-treated group exhibited a significantly higher proportion of moderately ill patients compared to the non-metformin-treated group (P = 0.0011). Nonetheless, no statistically significant differences were observed between the groups regarding oxygen support requirement or duration of hospital stay. Notably, the metformin group showed distinct variations in haematological parameters, including lower serum creatinine levels (P = 0.0049),

platelet count (P = 0.02) and HbA1c levels (P = 0.01). In conclusion, pre-existing metformin treatment did not impact the duration of hospital stay or the need for oxygen support in COVID-19 patients. However, the treatment did exert influence on other essential parameters.

Keywords: COVID-19; metformin; oral antidiabetic treatment; diabetes mellitus; therapeutic outcome; HbA1c

Graphical abstract



The figure depicts the study outline and key study outcomes. In brief, it was found that patients who were on metformin therapy during COVID-19 disease had significantly lower platelet count (however, in normal range), Serum creatinine levels and Glycated haemoglobin levels.

1. Introduction

Coronavirus disease (COVID-19) is a contagious disease typically leading to an upper respiratory tract infection caused by variants of SARS-COV-2 identified in Wuhan, China in December 2019.

The origin of SARS-CoV-2 remains unconfirmed, but it has affected over 200 countries, resulting in more than 114 million confirmed cases and 2.53 million deaths as of March 2021, making it one of the deadliest pandemics. India has reported 43.1 million cases and over 5.23 lakh deaths as of May 6, 2022 [1]. All age groups are susceptible, but children have a lower risk of infection. Males have a higher risk of severity and mortality compared to females. Older patients

with comorbidities are at higher risk. Patients with COVID-19 and type 2 diabetes have a greater risk of infection, complications, and mortality [2].

Research shows that patients with diabetes have an elevated risk of serious COVID-19 [3]. Metformin use in COVID-19 patients is associated with increased lactic acidosis risk but not mortality. Monitoring renal function, adjusting metformin dose, and considering COVID-19 status are advised [4]. Some studies show no benefit or increased death risk with metformin therapy [5–7], while others demonstrate better outcomes. Metformin and DPP-4 inhibitors can lead to positive outcomes with respect to decreased length of hospital stay and in-hospital mortality in hospitalized COVID-19 patients with diabetes [8]. Metformin use is correlated with improved clinical outcomes and early discharge [9,10]. It is associated with reduced mortality in women with COVID-19 and obesity or type 2 diabetes [11]. Survival chances are higher with metformin and acarbose treatment [12]. Metformin therapy may reduce mortality in patients with diabetes and chronic respiratory diseases [13]. Metformin activates AMPK signaling, inhibiting ACE2-viral spike protein binding and reducing viral entry. It also increases ACE2 stability, offering cardiopulmonary protection and reducing SARS-CoV-2 infection risk. Metformin suppresses inflammation, cytokine release, and oxidative stress, attenuating the immune response. It inhibits host-viral protein interactions, viral replication, and virion assembly. Metformin's effects reduce microvascular complications and thrombotic events during SARS-CoV-2 infection [14]. Further research is needed to assess the impact of antidiabetic drugs, particularly metformin, in COVID-19 patients with diabetes. We aim to evaluate the association between metformin use and therapeutic outcomes and the effect of metformin and non-metformin therapy on laboratory parameters.

2. Patients and methods

2.1. Study design

We examined medical records for patients admitted to Parul Sevashram Hospital in Vadodara, Gujarat, India, from July to December 2020. The study adhered to relevant laws and institutional guidelines and was approved by the institutional ethics committee of Parul Sevashram Hospital (Approval no. PUIECHR/PIMSR/O0/081734/3004). Data was collected from medical records of patients admitted during the specified period, and clinical outcomes were recorded. We included patients of both genders who were diagnosed with COVID-19 and Type 2 diabetes mellitus based on the disease classification (ICD-10). Patients with Type 1 diabetes mellitus or those above 85 years of age were excluded from the study. A sample size of 150 was estimated using Raosoft software, with an error margin of <5% and confidence interval >95%.

Demographic details such as age, gender, weight, date of admission, date of discharge, reason for admission, medical history, medication history, underlying disease, clinical severity, diagnosis, oxygen support category, diabetes status, duration of diabetes, laboratory tests, length of hospital stay, COVID-19 outcome and other relevant information (if available) were recorded. Patients were categorized based on clinical severity using the guidelines for Diagnosis and Treatment of Pneumonia Infected by Novel Coronavirus mentioned in Table 1 [15].

Table1. Criteria for categorization of clinical severity of patients.

Category of clinical severity	Criteria
Mildly ill	Mild symptoms with no indication of pneumonia shown on CT Scan
Moderately ill	Complaints of fever and respiratory symptoms with an indication of pneumonia found on CT Scan
Severely ill	Respiratory rate >30 breaths/minutes; resting oxygen saturation <93%; or PaO_2/FiO_2 ratio <300 mm Hg
Critically ill	Respiratory failure and mechanical ventilation, shock or intensive care required

2.2. Ethical issues

This retrospective observational study was conducted in accordance with the World Medical Association Declaration of Helsinki. The Parul University-institutional ethics committee on human research (PU-IECHR) reviewed, discussed and approved this study (PUIECHR/PIMSR/00/081734/3004). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

2.3. Statistical analysis

Microsoft Excel program was used to store and scrutinize the information followed by the statistical analysis of data in GraphPad Prism software. Association between categorical variables was analyzed using Fisher's exact test. Unpaired t-test was applied to compare the mean of variables between metformin and non-metformin group. This test allowed us to evaluate the significance of the difference between the two independent groups. All the data were presented as median and the number and percentage, as appropriate. A P-value <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics and co-morbidities

Out of the 150 COVID-19 patients analyzed in the study, 75 had metformin prescribed to them, while the rest did not. Of the total of 150 patients, 30 (40%) and 20 (26.6%) of the metformin group and non-metformin group participants were males (P = 0.11), while the other 45 (60%) and 55 (73.33%) were females, and the average age in the two groups were 56.49 and 56.18 years (P = 0.38), respectively. No significant difference was observed between the two groups with respect to pre-existing co-morbidities (Table 2).

Table 2. Comparison of co-morbidities among patients between the metformin and non-metformin group.

Co-morbidities	Metformin group/n (%)	Non-metformin group/n (%)	P-value
Hypertension	25 (33.33%)	27 (36%)	0.86
Ischemic heart disease	4 (5.33%)	0 (0%)	0.12
Chronic kidney disease	0(0%)	4 (5.33%)	0.12
Hypothyroidism	5(6.66%)	0 (0%)	0.05

3.2. Metformin and clinical severity of COVID-19

A significant difference in the clinical severity was found between metformin treated group and non-metformin treated group at the time of admission (P = 0.0011) as shown in Table 3.

Table 3. Comparison of clinical outcome of patients between the metformin treated group and non-metformin treated group.

Clinical outcome	Category	Metformin group (n = 75)	Non-metformin group (n = 75)	P-value
Clinical severity /n (%)	Mildly ill	55 (73.33%)	69 (92%)	0.0011
	Moderately ill	17 (22.66%)	2 (2.66%)	0.0011
	Severely ill	3 (4%)	4 (5.33%)	0.0011
Oxygen support category/n (%)	Ambient air	60 (80%)	59 (78.66%)	1.00 (Odds ratio = 1.085)
	Non-invasive oxygen support	15 (20%)	16 (21.33%)	1.00 (Odds ratio = 1.085)

3.3. Metformin and requirement of oxygen support

There was no difference in the oxygen support category between metformin group and non-metformin group (P = 1.00) as shown in Table 3.

3.4. Metformin and duration of hospitalisation

There was no significant difference found in the days of hospital stay between the two groups (P = 0.78) as shown in Table 4.

Table 4. Comparison of clinical outcome of patients between the metformin group and no-metformin group.

Hospitalization duration (days)	Metformin group (n = 75)	Non-metformin (n = 75)	P-value
(Mean ± SEM)	6.880 ± 0.3676	6.733 ± 0.3850	0.7833

Note: SEM: Standard error of mean.

3.5. Co-prescribed drugs

Drugs prescribed to the patients under study for blood glucose control, treatment of hypertension, antimicrobials etc. were recorded. All patients received strict anti-diabetic medications after admission. There was no significant difference in co-prescription of anti-diabetic medications between two groups. There was no significant difference between the groups with respect to use of antihypertensive therapy. All patients received antibacterial, antiviral, and appropriate supportive therapies after admission. There was no significant difference with respect to the use of antimicrobial agents between the two groups as shown in Table 5.

Table 5. Comparison of co-prescribed medications between the metformin and non-metformin group patients.

	Metformin group (75 patients)/n (%)	**Non-metformin (75 patients) /n (%)**	**P-value**
Antidiabetic treatment			
Glipizide	3(4%)	2(2.66%)	>0.99
Glibenclamide	3(4%)	2(2.66%)	>0.99
Voglibose	9(12%)	12(16%)	0.6388
Teneligliptin	19(25.33%)	23 (30.66%)	0.5857
Pioglitazone	8(10.66%)	5 (6.66%)	0.5633
Insulin	25(33.33%)	35(46.66%)	0.1333
Glimepiride	20 (26.66%)	31(41.33%)	0.0843
Antihypertensive treatment			
ACE inhibitors	2(2.66%)	0(0%)	>0.99
Thiazide Diuretics	4(5.33%)	6(8%)	0.74
Angiotensin-2 receptor blockers	6(8%)	8(12%)	0.58
Beta blockers	9(12%)	5(6.66%)	0.40
Calcium channel blockers	13(16%)	22(29.33%)	0.07
Drugs for COVID-19 treatment			
Hydroxychloroquine	75(100%)	74(98.66%)	>0.99
Doxycycline	8(10.66%)	15(20%)	0.1730
Oseltamivir	18(24%)	28(37.33%)	0.1105
Other drugs			
Statin	1(1%)	0(0%)	>0.99
Anticoagulant	10(14%)	9(12%)	0.81
Levofloxacin	10(13.33%)	19(25.33%)	0.09
Corticosteroid	5(6.66%)	13(17.33%)	0.07
Azithromycin	46(62.66%)	57(74.66%)	0.07
Ceftriaxone	10 (13.33%)	20 (29.33%)	0.0650

3.6. Other laboratory parameters

On admission, there was no difference in the WBC count (P = 0.69), aspartate transaminase (P = 0.21), alkaline phosphatase (P = 0.43), C-reactive protein (P = 0.71), lymphocytes (P = 0.06), eosinophils (P = 0.27), monocytes (P = 0.18), basophils (P = 0.15), serum urea (P = 0.07), random blood sugar

(P = 0.87), fasting blood sugar (P = 0.05), between two groups. One patient from metformin and 9 patients from non-metformin group had Blood Urea Nitrogen (BUN) levels above normal range. Significant difference in the level of platelet count (P = 0.02), serum creatinine (P = 0.0049) and HbA1c (P = 0.0108) was found between the groups (Table 6 and Figure 1).

Table 6. Comparison of laboratory parameters of patients between the metformin group and non-metformin group.

Laboratory parameters	Metformin group Mean (range) (n = 75)	Non-metformin Mean (range) (n = 75)	P-value
WBC	6809.00 (2840–17000)	6628.00 (2800–16760)	0.696
Platelet count (no./ µL)	247877.00 (91000–473000)	400055.00 (55000–3320000)	0.021
AST (U/L)	32.09 (10–422)	24.89 (11–63)	0.216
ALP (U/L)	61.77 (11–194)	64.80 (26–144)	0.437
Serum creatinine (µmol/L)	0.91 (0.4–1.7)	1.90 (0.5–13)	0.005
CRP (mg/L)	44.70 (1.73–177.9)	46.98	0.715
HbA1c (mmol/mol)	7.84 (5.5–13.6)	8.81 (5–15.20)	0.010
Lymphocytes (%)	24.67 (3–48)	21.84 (4–50)	0.060
Eosinophils (%)	2.34 (1–6)	2.60 (0–8)	0.266
Monocytes (%)	4.58 (0–12)	5.37 (0–29)	0.184
Basophils (%)	0 (0)	0(0–1)	0.151
S. urea (mmol/L)	28.56 (2.60–92)	35.74 (6–187)	0.073
RBS (mmol/L)	195.12 (80.66–377)	193.52 (104.0–335.6)	0.875
FBS (mmol/L)	168.78 (80–365)	188.63 (74.50–386)	0.056

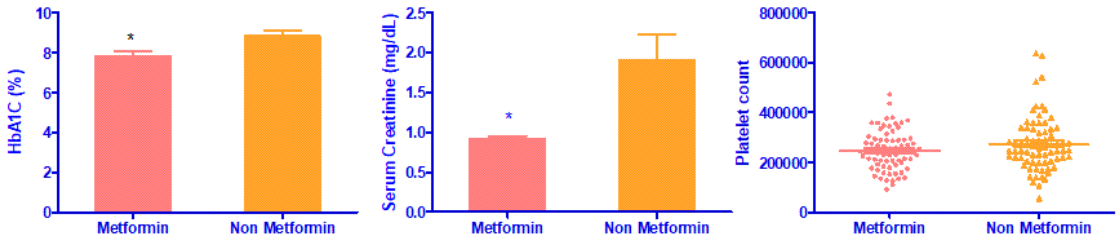


Figure 1. Comparison of HbA1C, serum creatinine values and platelet count between the metformin and non-metformin groups.

4. Discussion

In this retrospective study conducted for 6 months from the duration of July, 2020 to December, 2020 in Parul Sevashram Hospital, 150 patients with diabetes suffering from COVID-19 were included. Of the total 150 patients, 75 were metformin users and 75 were using anti-diabetic agents other than metformin. In our study, we observed no significant difference in patient age and gender between the groups being investigated. This finding contrasts with the study conducted by Alamin Alkundi et al., which reported a higher likelihood of hospitalization among male COVID-19 patients

compared to females [16]. Additionally, the study conducted by Pan Luo et al. similarly revealed no significant distinction between the two groups concerning age and gender [9].

There was a significantly higher number of metformin receiving patients who suffered from moderate disease as compared to non-metformin users. However, the duration of hospital stays or category of oxygen support required was not statistically different between the two groups. The lack of variance in hospitalization duration and oxygen support may be attributed to potential differences in the initial clinical condition of the patients in each group. There was no mortality observed in any of the cases. Based on our findings, we can conclude that the recovery of the metformin-treated group was comparable to that of non-metformin users, despite the initial higher disease severity observed in the metformin user group. This effect may be attributed to metformin's established anti-inflammatory activity, which can help mitigate the excessive immune response and cytokine storm associated with severe COVID-19 cases [17]. Furthermore, metformin has been found to improve endothelial function and reduce vascular complications [18], which are significant contributors to the severity of COVID-19 outcomes. These properties of metformin may have contributed to the better recovery observed in COVID-19 patients receiving metformin.

In addition to its anti-inflammatory and endothelial function benefits, metformin has been linked to the modulation of the renin-angiotensin-aldosterone system (RAAS). This modulation potentially reduces the risk of acute respiratory distress syndrome (ARDS) in COVID-19 patients. By influencing the ACE2/AngII/AT1R axis, metformin may play a role in preventing adverse respiratory complications and improving patient outcomes [19]. Apart from this, metformin alters the endosomal pH to slow down virion assembly and maturation [20]. These several beneficial effects may have played a role in better recovery of the COVID-19 patients with metformin. A study by Cheng et al. also demonstrated no difference in mortality among the metformin and non-metformin treated groups [4].

A significant difference between platelet count, serum creatinine level and HbA1c level among metformin and non-metformin groups was observed. Elevated platelet count above 4,50,000 per µL upturns the risk of venous thromboembolism which is one of the complications of COVID-19. In previous studies, metformin has shown to prevent disseminated intravascular coagulation by inhibiting platelet activation factor and mitochondrial DNA release [21]. The significantly low platelet level (within normal limit) in metformin treated patients is an added beneficial effect associated with metformin use. Metformin treated patients also had significantly lower serum creatinine levels as compared to patients in non metformin group. In their study, Cheng et al, however, did not find any such effect in metformin treated group [22]. Mrozikiewicz-Rakowska et al, observed the effect of insulin and metformin on various vital parameters in COVID-19 patients. They also recorded a smaller rise in serum creatinine levels in metformin treated patients as compared to insulin treated patients [23]. Improved serum creatinine levels in metformin treated patients are most likely to be associated with nephroprotective effect of metformin [24].

There was no significant difference observed between the days of hospitalization and type of oxygen support required between the two groups of patients. Moreover, previous studies have demonstrated a reduced mortality in metformin users Vs non users, there is no significant difference observed between oxygen support categories and length of hospital stay [4,8]. Metformin has proven anti-inflammatory activity via reduced production of cytokines and other inflammatory markers [25]. There were reduced circulating inflammatory biomarker levels in patients of COVID-19 who were on metformin therapy as compared with non-metformin users [26]. It has demonstrated potential as a

host directed therapy for treatment of COVID-19 [27]. The importance of host directed therapy is less relevant when it comes for modulation of disease severity or recovery (reflected as duration of hospital stay); rather it is expected to have significant impact on the death associated with COVID-19 complications. A Similar effect is reflected in the result of most of the studies, where clinical severity and length of hospital stay is not reduced but a significant reduction in mortality is observed.

In our study, although we have tried to minimize the confounding factors by statistical methods, the inherent variability associated with data obtained in a retrospective manner may affect the study outcomes. Thus, there is need of a prospective study which may draw a clearer picture of the role of metformin therapy in COVID-19 management.

5. Conclusions and limitations of the study

In conclusion, we demonstrated that pre-existing metformin therapy in COVID-19 patients with diabetes does not affect duration of hospital stay or type of oxygen support required when compared with metformin non-users. However, there was improvement in parameters like HbA1c, serum creatinine and platelet count among the groups which may have beneficial effects on disease outcome.

We evaluated COVID-19 patient data from a specific time period. A modified virus characteristics over time may limit the direct generalization of the study results. The retrospective nature of the study introduced reliance on existing data with varying quality and recall bias, limitations in controlling for confounding variables, temporal ambiguity, and a restricted ability to establish causality. Moreover, this study was conducted on limited sample data for only patients admitted in the hospital, which may pose a limitation with respect to generalization of the study results.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflicts of interest

All authors declare no conflicts of interest in this paper.

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