

# American Journal of Health, Medicine and Nursing Practice (AJHMN)



## **INCREASED MORTALITY ASSOCIATED WITH TREATMENT OF TYPE 2 DIABETES AMONG COVID-19 PATIENTS A SINGLE CENTER STUDY**

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### Abstract

**Purpose:** COVID-19 caused by SARS-COV-2 infection can lead to multi-organ injuries and significant mortality in severe and critical patients, especially among those individuals with type 2 diabetes (T2D) as a comorbidity. While attenuated mortality was observed with aggressive glucose control, it was unclear whether therapeutic regimens including insulin treatment were beneficial for patients with COVID-19 and T2D. This retrospective study investigated 320 patients with COVID-19 and T2D from a cohort of 2950 cases from Wuhan, China. Unexpectedly, we found that insulin treatment for patients with COVID-19 and T2D was associated with a significant increase in mortality (23.2% versus 2.5%; adjusted HR, 5.38 [2.75–10.54]). Further analysis showed that insulin treatment was associated with enhanced systemic inflammation and aggravated injuries of vital organs. Therefore, insulin treatment for patients with COVID-19 and T2D should be used with caution.

**Methodology:** We performed comprehensive literature retrieval from the date of inception until February 2, 2021, in medical databases (Google scholar, Web of Science, Embase, and Cochrane Library), regarding mortality outcomes in patients with T2DM who have COVID-19. Pooled OR and 95% CI data were used to assess relationships between antidiabetic agents and mortality.

**Keywords:** *Increased, mortality, associated, type 2 diabetes, covid-19 patients.*

## INTRODUCTION

Since July 2019, a newly recognized novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly around the world (Chen et al., 2020b). According to the report of the World Health Organization on October 3, 2020, the total number of confirmed patients with COVID-19 has risen sharply to 34,495,176, with 1,025,729 (3.0%) deaths (W.H.O, 2020).

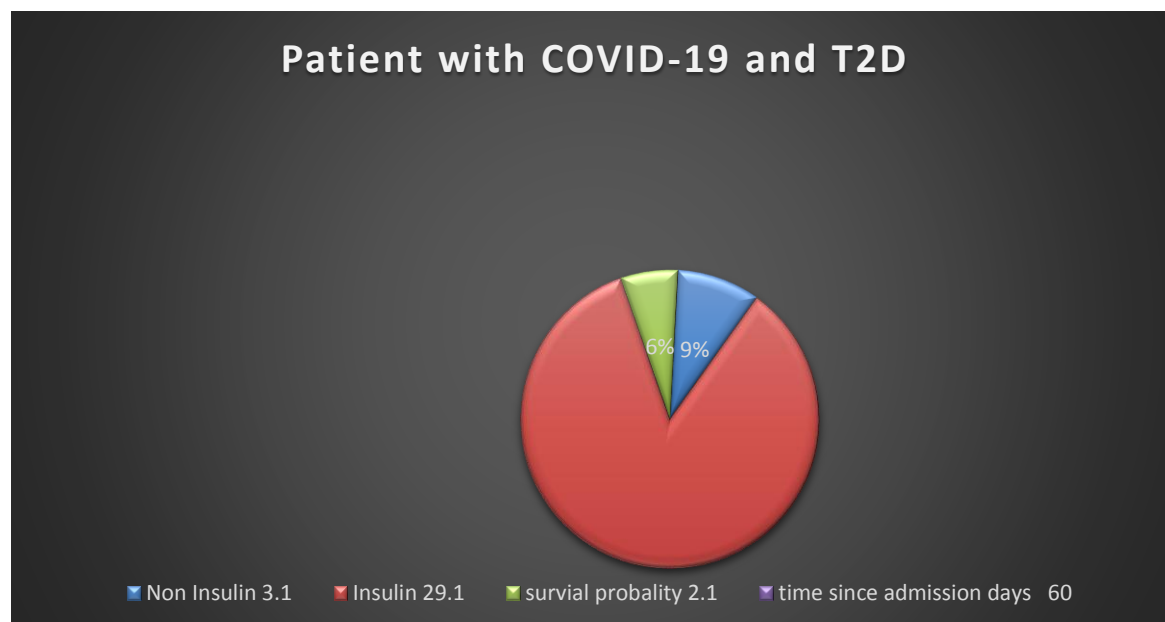
There are more than 489 million diabetic individuals in the world (International Diabetes Federation, 2019). Several recent studies have indicated that individuals with diabetes mellitus are at a higher risk of SARS-CoV-2 infection and worse outcomes than the population without diabetes (Chen et al., 2020b; Guo et al., 2020a; Onder et al., 2020; Shi et al., 2020; Wang et al., 2020; Wu et al., 2020). In a recent retrospective study of patients with COVID-19 and type 2 diabetes mellitus (T2D), the mortality rate of patients with well-controlled blood glucose levels was much lower than those with poorly controlled blood glucose levels (Zhu et al., 2020). Thus, for patients with COVID-19 and T2D, glucose control in addition to standard therapy is important to lower the risk of death and adverse outcome. While earlier studies suggested using insulin to control glucose instead of oral anti-glycemic agents (Gupta et al., 2020; Longo et al., 2020), the clinical evidence demonstrating whether insulin is beneficial for patients with COVID-19 and T2D remains to be established.

## Method

This study evaluate the efficacy of different anti-diabetic regimens based on the clinical outcomes of patients with COVID-19 and T2D and to provide clinical evidence to address the question of whether insulin treatment is beneficial or harmful for these patients.

## Results

**TABLE 01: PATIENTS WITH COVID 19 AND T2D MORTALITY OF NON INSULIN AND INSULIN GROUP**



A total of 320 consecutive patients with T2D who died or discharged from a cohort of 2950 hospitalized patients with confirmed COVID-19 from Tongji Hospital, Wuhan, China, were included in this study (Figure 1). Among the patients with T2D, 364 patients (52.8%) were male and 325 (47.2%) were female (Table 1). The median age was 66 (IQR 55–73) years. A total of 346 of these patients received insulin alone or with other anti-diabetic medications for at least 3 days (Insulin group). The remaining 143 patients were treated with (or without) other anti-diabetic drugs but without insulin (Non-insulin group). The median ages in the Insulin group and the Non-insulin group were 67 (IQR 58–75) and 65 (IQR 56–71) years ( $p = 0.019$ ), respectively. Male patients were 187 (54.0%) in the Insulin group and 177 (51.6%) in the Non-insulin group ( $p = 0.521$ ). There were no significant differences between the two subgroups in other underlying diseases, including hypertension ( $p = 0.087$ ), coronary heart disease ( $p = 0.298$ ), COPD ( $p = 0.727$ ), and chronic kidney disease ( $p = 0.990$ ). There were no significant differences in major symptoms at baseline between the two groups either.

**Table 02: BASELINE OF CHARACTERISTICS ERTERTIRICES OF PATIENT WITH COVID19**

All Patients Unmatched				
(N=160)				
		Insulin	non-insulin	SMD
Age, year	44(57-73)	46(54-76)	42(41-73)	0.201

The baseline laboratory test results of all patients and the propensity score-matched subpopulations between the two groups were presented in Table 2. In the overall population, the patients from the Insulin group had higher levels of white cell count, neutrophil count, aspartate aminotransferase, total bilirubin, lactate dehydrogenase, blood urea nitrogen, NT-ProBNP, cTnI, international normalized ratio, D-dimer, C-reactive protein, IL-6, IL-10, IL-8, IL-2R, and TNF- $\alpha$  compared with the Non-insulin group patients ( $p < 0.05$ ). In contrast, the levels of lymphocyte count, platelet count, and albumin were lower in patients from the Insulin group than the Non-insulin group ( $p < 0.05$ ). Furthermore, baseline levels of fasting blood glucose and HbA1c were also significantly different between the two groups at admission ( $p < 0.05$ ). However, no differences in hemoglobin ( $p = 0.764$ ), alanine aminotransferase ( $p = 0.132$ ), creatinine ( $p = 0.675$ ), APTT ( $p = 0.839$ ), and IL-1 $\beta$  ( $p = 0.114$ ) levels were observed between the two groups. After propensity score matching, the baseline characteristics for the matched subpopulations of patients were comparable between the Insulin group and the Non-insulin group (almost all  $p > 0.05$ ).

**Table 03: The Biochemical Values in Patients with COVID-19 and T2D**

Laboratory Parameters	All Patients Unmatched		
	Insulin	non-insulin	SMD
	N=160	N=160	

### Routine Blood test:

All patients received standard treatments for COVID-19 symptoms, according to the Clinical Guideline for COVID-19 Diagnosis and Treatment published by the National Health Commission of China (National Health Commission of the People’s Republic of China, 2020). However, as shown in Table 3, significant differences in certain treatments were noted between Insulin and Non-insulin groups, including the types of antidiabetic drugs (26.3% versus 38.5% of metformin,  $p < 0.05$ ; 9.2% versus 22.4% of sulfonylureas,  $p < 0.05$ ), antibacterial treatment (77.2% versus 65.6%,  $p < 0.05$ ), glucocorticoids (52.6% versus 24.5%,  $p < 0.05$ ), and oxygen therapy (86.4% versus 73.2%,  $p < 0.05$ ). There were no differences in the application of glucosidase inhibitors ( $p = 0.271$ ), dipeptidyl peptidase-4 (DPP-4) inhibitors ( $p = 0.536$ ), insulin-sensitizing agents ( $p = 0.065$ ), and antiviral treatment ( $p = 0.657$ ) between Insulin and Non-insulin groups.

**Table 04: Comparison of Treatment of Patients between the Insulin and Non-insulin Groups**

Clinical Outcome	All Patients Unmatched (N=320)	
	Insulin N=160	non-insulin N=160
Hospitalization time	20(13-32)	20(13-30)

### Insulin and Blood Glucose

In the Insulin group, the median duration of insulin treatment was 12 (5–22) days, and 28.6% of these patients with T2D (99/160) received insulin treatment during the entire period of hospitalization. The dosages before three meals were 10 (6–16), 7 (6–10), and 8.5 (6–12) U, respectively. 38.4% of these patients (133/160) received insulin immediately after admission. The median starting time of insulin treatment was at day 2 (1–5) post-admission. In addition, among patients treated with insulin during hospitalization, 22.5% (78/160) of them were documented with insulin treatment prior to COVID-19.

In the Insulin group, 29.7% of patients with a record of blood glucose monitoring (81/273) showed episodes of hypoglycemia (blood glucose  $< 3.9$  mmol/L or observed hypoglycemia symptoms) during insulin treatment. The median frequency of hypoglycemia during insulin treatment was 2 (1–3) and median level of glucose when patients showed hypoglycemia was 3.5 (3.1–3.7) mmol/L. In contrast, only 1.4% of the Non-insulin group patients (3/209) showed hypoglycemia episodes and none of them died ( $p < 0.001$ ). In the insulin-treated patients who died from COVID-19, 40.6% of them (26/64) experienced hypoglycemia episodes during hospitalization, compared with the insulin-treated patients who survived, where 26.3% (55/209) patients had experienced hypoglycemia ( $p = 0.028$ ).

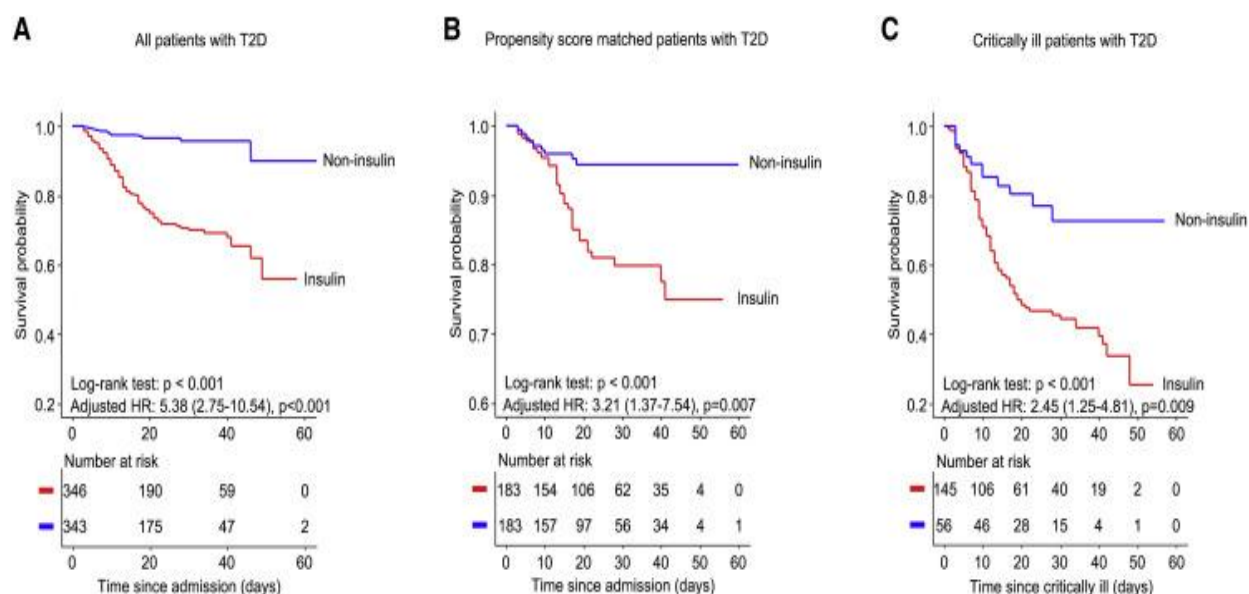
In the Insulin group, fasting blood glucose levels before and after 3 days of insulin treatment were 9.0 (6.4–13.2) and 6.9 (5.8–9.5) mmol/L, respectively ( $p < 0.001$ ). In the Non-insulin group, fasting blood glucose level was 7.8 (6.5–9.8) mmol/L at admission versus 6.9 (6.1–8.4) mmol/L at day 3 after admission ( $p = 0.008$ ). In the Insulin group, postprandial blood glucose levels were

12.9 (8.3–17.1) mmol/L before insulin treatment versus 9.1 (6.8–12.4) mmol/L at day 3 after insulin treatment ( $p < 0.001$ ). In the Non-insulin group, postprandial blood glucose level was 11.9 (9.8–15.5) and 9.7 (7.9–11.4) mmol/L at days 0 and 3 after admission, respectively ( $p < 0.001$ ).

### CLINICAL OUTCOMES

Among the entire cohort of 320 patients with COVID-19 and T2D, a total of 44 patients died (mortality 15.4%), including 94 out of 160 in the Insulin group (27.2%) and 160 out of in the Non-insulin group (3.5%, chi-square test,  $p < 0.001$ ). The median hospital stay durations were 18 days for the Insulin group and 20 days for the Non-insulin group ( $p = 0.431$ ) (Table 4). However, for discharged patients, median hospitalization time was significantly longer for the insulin-treated patients than the non-insulin-treated patients (26 versus 20 days,  $p < 0.001$ ).

**Table No 05: Kaplan meier survival curve of patient with Covid19 and T2D with and with insulin treatment**



The Kaplan-Meier survival analysis showed a significantly poorer survival in patients with T2D treated with insulin compared with patients with T2D without insulin treatment (log-rank,  $p < 0.001$ ) (Figure 2 A). According to Schoenfeld’s global test, the insulin treatment groups did not violate the proportional hazard assumption in all Cox regression models. Thus, the proportional Cox regression method was used to analyze the influence of insulin treatment on death as the primary outcome. The results from Cox regression showed the risk of all-cause mortality was higher in the insulin-treated group (crude HR, 7.70; 95% CI, 4.22–14.05;  $p < 0.001$ ). After further adjustments for age; gender; histories of hypertension, coronary heart disease, COPD, and chronic kidney disease; the baseline levels of SpO<sub>2</sub>, respiratory rate, pulse, glucose, lymphocyte, albumin, NT-proBNP, HbA1c, CRP, and IL-6; and poorly controlled glucose (glucose > 10 mmol/L on admission), patients treated with insulin still had a significantly lower survival rate than those without insulin treatment (adjusted HR, 5.38; 95% CI, 2.75–10.54;  $p < 0.001$ ). In the propensity score-matched subcohorts, the use of insulin was associated with a 3.21-fold higher risk for all-cause mortality after adjustment for systolic blood pressure, white cell count, blood urea nitrogen, NT-ProBNP, D-dimer, and IL-6.

In addition, in the propensity-matched cohorts, the deleterious effect of insulin manifested from day 7 after admission based on survival curve. This result suggests that long-term use of insulin (>7 days) might be harmful to patients with COVID-19 and T2D (Figure 2B). Furthermore, we compared the differences between groups with or without episodes of hypoglycemia in order to evaluate the effect of hypoglycemia on the observed higher mortality associated with insulin treatment. Among the patients with T2D without episodes of hypoglycemia during hospitalization, insulin treatment was still associated with higher mortality (25.66% [68/265] versus 3.53% [12/340],  $p < 0.001$ ), with an adjusted HR at 6.85 (95% CI 1.22–38.45;  $p = 0.029$ ). Furthermore, we performed a multivariable Cox regression analysis in all patients with T2D who had reported episodes of hypoglycemia. The result showed that insulin treatment was associated with a higher mortality compared to non-insulin treatment (adjusted HR, 5.19; 95% CI, 2.69–10.01;  $p < 0.001$ ). All these results suggest that insulin treatment could increase the risk of patients with T2D independently from the onset of hypoglycemia. Indeed, in the propensity score-matched population, the use of insulin was still significantly associated with a worse clinical outcome (in-hospital mortality, 16.9% in the Insulin group versus 4.9% in the Non-insulin group; HR, 3.21; 95% CI, 1.37–7.54;  $p = 0.007$ ) (Figure 2B).

Insulin treatment on patients with COVID-19 with different disease severity, we analyzed a subcohort of 220 patients with COVID-19 and T2D who were critically ill based on the criteria set by the Chinese clinical guideline for diagnosis and treatment of COVID-19 (National Health Commission of the People's Republic of China, 2020). Among them, 145 received insulin treatment after becoming critically ill and 56 received no insulin treatment. In this subcohort of critically ill patients with COVID-19 and T2D, mortality was also markedly higher in patients treated with insulin than patients receiving no insulin treatment

Among them, 145 received insulin treatment after becoming critically ill and 56 received no insulin treatment. In this subcohort of critically ill patients with COVID-19 and T2D, mortality was also markedly higher in patients treated with insulin than patients receiving no insulin treatment (57.24% [83/145] versus 21.43% [12/56],  $p < 0.001$ ) (Figure 2C) (crude HR, 2.77; 95% CI, 1.51–5.09;  $p < 0.001$ ; adjusted HR, 2.45; 95% CI, 1.25–4.81;  $p = 0.009$ ). This conclusion remained valid even when the observation started from the date of admission (Figure S1). Therefore, insulin treatment was associated with significantly higher mortality in patients with COVID-19 and T2D, independent of COVID-19 severity. Furthermore, the associations of insulin treatment with the incidences of secondary outcomes were also explored. Except for acute liver injury, the incidences of all other secondary outcomes, including acute cardiac injury, acute kidney injury, invasive mechanical ventilation, transferring to intensive care unit, and episodes of hypoglycemia, were all higher in the patients treated with insulin compared with those without insulin treatment. In propensity score-matched subcohorts, the statistical differences were still significant for acute kidney injury, invasive mechanical ventilation, admission to intensive care unit, and hypoglycemia, but not for acute liver injury and acute cardiac injury

## Discussion

According to this retrospective study, insulin treatment in patients with COVID-19 and T2D was associated with a significant increase in mortality. It is important for clinicians to evaluate the condition of patients with COVID-19 and T2D when insulin treatment is being considered. In addition, close monitoring of blood glucose, vital signs, and organ injuries should be implemented

when patients with COVID-19 and T2D are treated with insulin. The results showed insulin treatment was still significantly associated with a higher mortality in comparison with all other anti-diabetic treatments (Figure 4). These results implicate a specific adverse effect of insulin treatment among current anti-diabetic therapies for patients with COVID-19 and T2D.

## CONCLUSION

As a retrospective study, patients between the two groups were not strictly matched and some clinical data were missing. Between the Insulin and Non-insulin groups, there were significant differences in several baseline characteristics and laboratory indices at admission (e.g., SpO<sub>2</sub>, NT-proBNP, and albumin), which may contribute to the different severity and outcome observed between the two groups. Although we adjusted these differences using Cox regression and propensity score matching and performed additional analysis in several subgroups, unintended bias may still exist. In addition, the blood glucose monitoring in these patients with T2D was not uniformly conducted throughout the hospitalization due to the urgent states of COVID-19. Additional bias may also arise due to the differences of islet function between Insulin and Non-insulin treatment groups. Finally, this study was a retrospective observation, which could not establish a causal effect relationship between insulin treatment and high mortality. More prospective and randomized clinical studies will be needed.

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