Metformin significantly lowers the mortality rate in diabetic COVID-19 patients

Ramazan Korkusuz (✉ ramazankorkusuz@hotmail.com)

University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology <https://orcid.org/0000-0002-9988-9596>

Faruk Karandere

Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey
<https://orcid.org/0000-0002-7423-0170>

Fatih Okay

Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey
<https://orcid.org/0000-0001-9901-5795>

Hakan Koçoğlu

Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey
<https://orcid.org/0000-0002-9208-2693>

Research Article

Keywords: COVID-19, diabetes mellitus, mortality, metformin, HbA1c

Posted Date: December 21st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1182263/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Introduction: This study evaluates the effect of glycemic control and anti-diabetic agents on the prognosis of diabetic COVID-19 patients.

Method: The study includes diabetic patients who were treated and followed up in our hospital because of COVID-19 between 1 June 2020 and 1 January 2021. Patients with any additional comorbidity were excluded from the study. The demographic data of the patients, physical examination findings, laboratory tests, and radiological examination results were obtained retrospectively from the hospital records system.

Results: A total of 207 diabetic patients consisted of 125 (60.4%) males and 82 (39.6%) females were included to this study. The mortality rate in cases using metformin was found to be statistically significantly lower than in cases using other drugs ($p=0.016$; $p<0.05$). No statistically significant difference was found between the HbA1c and glucose measurements of the cases according to mortality ($p>0.05$).

Discussion: Metformin treatment in diabetic patients diagnosed with COVID-19 should not be stopped, other than in cases with severely hypoxic advanced stage chronic renal failure. Metformin can be recommended as a preventative drug to increase survival in diabetic patients with COVID-19. Nevertheless, there is a need for more evidence and more extensive studies to investigate the protective effects of metformin in COVID-19 patients and in similar viral infections.

Introduction

Although the majority of cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) virus infection causing coronavirus disease 2019 (COVID-19) have an asymptomatic course, it is characterised by a wide range of clinical presentations, which can be serious and potentially fatal (1, 2). This disease is a significant cause of morbidity and mortality throughout the world and a significant increase has been determined in the sensitivity, severity, and hospitalisation and mortality rates of males, the elderly and those with comorbidities (hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus (DM), cancer, or chronic renal failure) (3–6).

In Turkey and throughout the world, there is an increase in the prevalence of diabetes mellitus, which is a leading cause of early disease and mortality, and diabetic individuals now constitute a significant proportion of national and global populations (7, 8). It has been determined that complications related to diabetes, which are an important cause of morbidity and mortality, can be significantly reduced with good glycemic control (9). Although the reason has not been fully revealed, as it has been observed that infections cause greater morbidity and mortality in diabetic patients compared to the normal healthy population, attention has been drawn to diabetic patients with COVID-19 (10–12).

Previous studies have observed a significant increase in mortality rates in diabetic individuals with COVID-19 compared to the general population (2, 13). Good glycemic control can potentially affect the prognosis and outcomes of COVID-19 infection. In cases with complex hyperglycemia, such as conditions clustered with diabetes in the context of metabolic syndrome such as obesity and hypertension, or cardiovascular disease or chronic kidney disease, these have been associated with a poor prognosis (14, 15). Patients with type 2 diabetes constitute approximately 90% of all diabetic individuals (16). A significant proportion of type 2 diabetic patients are treated with metformin, either alone or in combination.

Another important patient group is those who have used dipeptidyl peptidase-4 (DPP4) inhibitors and sodium glucose co-transporter-2(SGLT2) inhibitors in recent years, either alone or in combination with metformin. While metformin has some anti-inflammatory and anti-thrombotic effects independently of the diabetic status, DPP4 inhibitors have been shown to reduce virus entry and replication in the airway (17–19).

The aim of this study was to evaluate the effect of glycemic control and anti-diabetic agents on the prognosis of diabetic COVID-19 patients with no other comorbidity.

Material And Method

Study design and participants

The hospital where this study was conducted is the largest pandemic centre in Istanbul, opened in the first wave of the pandemic to accept only COVID-19 patients. The study included patients with a diabetic diagnosis who were treated and followed up in our hospital because of COVID-19 between 1 June 2020 and 1 January 2021. Patients with any additional comorbidity were excluded from the study. All the patients included had a positive result in reverse transcriptase polymerase chain reaction (RT-PCR) analysis of nasopharyngeal smear samples.

Approval for this retrospective study was granted by the Ethics Committee of Bakirkoy Sadi Konuk Training and Research Hospital, and the National Ethics Committee (decision no:2020/191). All procedures were in compliance with the Helsinki Declaration and its later amendments or comparable ethical standards.

Data Collection

The demographic data of the patients, physical examination findings, laboratory tests and radiological examination results were obtained retrospectively from the hospital records system. Disease severity of the cases was classified in 4 groups as defined by the World Health Organisation (WHO) (20).

The patients were separated into 4 groups of mild, moderate, severe, and atypical involvement according to the bilateral typical involvement of pneumonia on thoracic computed tomography images. For all the

patients, the results were recorded of Hb1Ac, glucose, full blood count, C-reactive protein, and other routine biochemical and microbiological tests performed at the time of presentation.

Statistical Analysis

Data obtained in the study were analyzed statistically using Number Cruncher Statistical System (NCSS) software. Descriptive statistical methods were used in the evaluation of the data and results were stated as mean±standard deviation (SD), median, minimum and maximum values, or as number (n) and percentage (%). In the comparison of two groups of quantitative data showing normal distribution, the Student's t-test was used and for two groups not showing normal distribution, the Mann Whitney U-test was applied. For the comparison of more than two groups of quantitative data not showing normal distribution, the Kruskal Wallis test was used. In the comparisons of qualitative data, the Pearson Chi-square test, Fisher's Exact test, and the Fisher-Freeman-Halton test were applied. A value of $p < 0.05$ was accepted as statistically significant.

Results

From a total of 344 diabetic patients with HbA1c data who were hospitalised and followed up between 1 June 2020 and 1 January 2021, evaluation was made in this study of 207 patients with no additional comorbidity comprising 125 (60.4%) males and 82 (39.6%) females with a mean age of 59.60 ± 12.02 years (range, 27-88 years). The length of hospital stay of the patients in the study was determined as mean 13.66 ± 8.08 days (range, 3-55 days). As a result of CT examination, 6 (2.9%) cases were determined with atypical findings, 54 (26.1%) with mild, 84 (40.6%) with moderate, and 60 (29%) with severe findings. Mortality developed in 12 (5.8%) cases and 195 (94.2%) were discharged. The disease course was observed to be moderate in 82 (39.6%) cases, severe in 101 (48.8%), and critical in 24 (11.6%).

No drugs were used by 50 (24.2%) cases, 1 drug by 56 (27.1%), 2 drugs by 33 (15.9%), and 3 or more drugs by 68 (32.9%). Of the cases using drugs, 121 (77.1%) were taking metformin, 46 (29.3%) sulfonylurea, 3 (1.9%) acarbose, 71 (45.2%) Dpp-4, 22 (14%) pioglitazone, 26 (16.6%) sglt-2, and 66 (42%) insulin.

The HbA1c measurement of the cases in the study was measured as mean $9.14 \pm 2.31\%$, glucose as 246.11 ± 113.98 mg/dl, hemoglobin as 12.85 ± 1.78 g/dl, hematocrit as $38.38 \pm 4.62\%$, leukocytes as 7659.58 ± 3916.84 $10^3/\mu\text{L}$, lymphocytes as 1303.94 ± 782.42 $10^3/\mu\text{L}$, neutrophils as 5830.63 ± 3526.06 $10^3/\mu\text{L}$, eosinophils as 47.34 ± 108.03 $10^3/\mu\text{L}$, thrombocytes as 231.83 ± 104.14 $10^3/\mu\text{L}$, AST as 43.23 ± 29.35 U/L, ALT as 37.3 ± 32.91 IU/L, urea as 43.01 ± 20.52 mg/dL, creatinine as 3.71 ± 0.46 mg/dL, LDH as 355.15 ± 149.51 U/L, ferritin as 404.29 ± 447.21 $\mu\text{g/L}$, triglycerides as 151.08 ± 86.52 mg/dl, CK as 199.43 ± 429.73 U/L, procalcitonin as 0.98 ± 6.21 ng/mL, CRP as 106.56 ± 78.55 mg/L, fibrinogen as 494.06 ± 116.56 mg/dL, PT as 14.12 ± 6.45 , APTT as 36.28 ± 7.56 secs, and D-dimer as 0.66 ± 1.18 $\mu\text{g/dL}$.

No statistically significant difference was determined in the age of cases according to mortality ($p > 0.05$). No statistically significant difference was determined in the mortality rates according to gender ($p > 0.05$).

No statistically significant difference was determined in the HbA1c measurements of cases according to mortality ($p>0.05$). No statistically significant difference was determined in the mortality rates according to the drug use status ($p>0.05$).

The mortality rates of patients using metformin were determined to be statistically significantly lower than those of patients using other drugs ($p=0.016$, $p<0.05$). No statistically significant difference was determined in the mortality rates in patients using sulfonylurea, acarbose, dpp-4, pioglitazone, sglt-2 and insulin ($p>0.05$). No statistically significant difference was determined between the HbA1c values of the cases according to the CT results ($p>0.05$). No statistically significant difference was determined between the HbA1c values of the cases according to the disease course. No statistically significant difference was determined in respect of the drug use status of the cases according to the disease course ($p>0.05$).

Significant differences were determined in the rates of metformin use according to disease course ($p=0.012$, $p<0.05$). The rate of metformin use by patients with a critical disease course was determined to be statistically significantly lower compared to cases with moderate and severe disease course. No statistically significant difference was determined in the rate of use of sulfonylurea, acarbose, dpp-4, pioglitazone, sglt-2, and insulin according to disease course ($p>0.05$).

Discussion

Age is a known risk factor for mortality in COVID-19 infection, and although the elderly diabetic patients in this study were seen to be at a greater risk of mortality, it was not at a statistically significant level. Previous studies have reported that mortality is higher in male patients (2). However, in the current study, no statistically significant difference was seen between the genders of the diabetic patients in respect of COVID-19-related mortality. As a result of a series of different mechanisms in diabetic patients, such as hypercoagulability, increased inflammation, hyperglycemia and impaired activation of the renin-angiotensin-aldosterone system (RAAS), COVID-19 infection is thought to increase morbidity and mortality irrespective of other underlying diseases (13, 21, 22). Diseases such as hypertension, cardiovascular disease and chronic renal disease, which are risk factors for COVID-19 mortality, make chronic glycemia more complicated. Therefore, when discounting risk factors in this study, HbA1c alone was not seen as a risk factor, and consistent with previous studies, did not affect mortality (23, 24).

Metformin, which is obtained from the *Galega officinalis* plant, is used as an anti-diabetic agent and in the treatment of malaria and influenza (25, 26). In a meta-analysis of diabetic patients, those using metformin were determined to have a significantly lower mortality rate during sepsis compared to those not using metformin (27). Some studies have suggested that metformin has an anti-inflammatory and anti-thrombotic effect (18, 28). It has also been thought that with similar effects, morbidity and mortality are decreased in COVID-19 patients (29).

In the current study, the use of metformin before COVID-19 infection was determined to be associated with a significant decrease in disease severity and mortality rates. A similar relationship was not determined in respect of the other diabetic drugs (insulin and other oral antidiabetics). Moreover, no

significant relationship was determined between the HbA1c level and mortality. The fact that there was no significant correlation with HbA1c and that similar results were obtained to those of different previous studies, showed that apart from the antihyperglycemic effect, the different effects of metformin decreased mortality (23, 24, 30, 31). As such similar results have been obtained in different populations from around the world, this suggests that the observed reduction in the risk of death associated with the use of metformin in subjects with diabetes and COVID-19 may be generalizable.

In conclusion, as far as possible, metformin treatment in diabetic patients diagnosed with COVID-19 should not be stopped, other than in cases with severely hypoxic advanced stage chronic renal failure. Metformin can be recommended as a preventative drug to increase survival in diabetic patients with COVID-19. Nevertheless, there is a need for more evidence and more extensive studies to investigate the protective effects (anti-hyperglycemic, antiviral, anti-inflammatory, and anti-thrombotic) of metformin in COVID-19 patients and in similar viral infections.

Declarations

Authors contributions

Conceived and designed the review: RK,FK,HK; Performed the search of articles: RK, FK; Read the literature and applied the exclusion criteria: FK,HK; Substantial contribution to interpretation of data: HK,FK; Gathered the information and valid biomarkers from the articles: RK,FK; Wrote the manuscript: HK, RK. All authors critically revised the manuscript for important intellectual content, approved the final the version to be submitted and agreed to be accountable for the content of the manuscript.

Competing interests

The authors declare no competing interests.

References

1. -Oran DP, Topol EJ. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic: A Systematic Review. *Ann Intern Med*. 2021 Jan 22:M20-6976. doi: 10.7326/M20-6976. Epub ahead of print. PMID: 33481642; PMCID: PMC7839426.
2. -Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020 Apr 7;323(13):1239-1242. doi: 10.1001/jama.2020.2648. PMID: 32091533.
3. -Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, Yu X, Dong K. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. *BMJ Open Diabetes Res Care*. 2020 Apr;8(1):e001343.
4. -Apicella M. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol*. 2020;8:782–792.

5. -Zhou F. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062.
6. -Erdal GS, Polat O, Erdem GU, Korkusuz R, Hindilerden F, Yilmaz M, Yasar KK, Isiksacan N, Tural D. The mortality rate of COVID-19 was high in cancer patients: a retrospective single-center study. *Int J Clin Oncol*. 2021 May;26(5):826–834.
7. -Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, Karsidag K, Genc S, Telci A, Canbaz B, Turker F, Yilmaz T, Cakir B, Tuomilehto J; TURDEP-II Study Group. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. *Eur J Epidemiol*. 2013 Feb;28(2):169–80. doi: 10.1007/s10654-013-9771-5
8. -International Diabetes Federation. IDF Diabetes Atlas, 9th ed, 2019. Available at: <https://www.diabetesatlas.org> (Accessed on March, 2021)
9. -Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998 Sep 12;352(9131):854-65. Erratum in: *Lancet* 1998 Nov 7;352(9139):1558. PMID: 9742977.
10. -Abu-Ashour W, Twells LK, Valcour JE, Gamble JM. Diabetes and the occurrence of infection in primary care: a matched cohort study. *BMC Infect Dis* 2018; 18:67.
11. -Carey IM, Critchley JA, DeWilde S, et al. Risk of Infection in Type 1 and Type 2 Diabetes Compared With the General Population: A Matched Cohort Study. *Diabetes Care* 2018; 41:513.
12. -Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, Xu X, Xu XP, Chan JC. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med*. 2006 Jun;23(6):623-8. doi: 10.1111/j.1464-5491.2006.01861.x. PMID: 16759303
13. -Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, Knighton P, Holman N, Khunti K, Sattar N, Wareham NJ, Young B, Valabhji J. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol*. 2020 Oct;8(10):813–822. doi: 10.1016/S2213-8587(20)30272-2. Epub 2020 Aug 13. PMID: 32798472; PMCID: PMC7426088.
14. -Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 395:1054–1062.
15. -Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, Aaron JG, Claassen J, Rabbani LE, Hastie J, Hochman BR, Salazar-Schicchi J, Yip NH, Brodie D, O'Donnell MR. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet* 395:1763–1770.
16. -American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. *Diabetes Care* 2018; 41:917.
17. -Pernicova I, Kelly S, Ajodha S, Sahdev A, Bestwick JP, Gabrovskaa P, Akanle O, Ajjan R, Kola B, Stadler M, Fraser W, Christ-Crain M, Grossman AB, Pitzalis C, Korbonits M. Metformin to reduce metabolic

- complications and inflammation in patients on systemic glucocorticoid therapy: a randomised, double-blind, placebo-controlled, proof-of-concept, phase 2 trial. *Lancet Diabetes Endocrinol.* 2020 Apr;8(4):278–291. doi: 10.1016/S2213-8587(20)30021-8. Epub 2020 Feb 25. PMID: 32109422
18. -Cameron AR, Morrison VL, Levin D., Mohan M., Forteath C., Beall C. Anti-inflammatory effects of metformin regardless of diabetes status. *Circ Res.* 2016; 119: 652–665
 19. -Solerte SB, D'Addio F, Fiorina P. Reply to letter to the editor regarding "Use of DPP-4 inhibitors in patients with COVID-19". *Acta Diabetol.* 2021 Feb;58(2):247–248. doi: 10.1007/s00592-020-01630-5. Epub 2020 Nov 17. PMID: 33201344; PMCID: PMC7669486
 20. -World Health Organization. (2021). COVID-19 clinical management: living guidance, 25 January 2021. World Health Organization. <https://apps.who.int/iris/handle/10665/338882>. License: CC BY-NC-SA 3.0 IGO Accessed 30 April 2021
 21. -Tadic M, Cuspidi C, Sala C. COVID-19 and diabetes: Is there enough evidence?. *J Clin Hypertens (Greenwich).* 2020;22(6):943–948. doi:10.1111/jch.13912.
 22. -Patel VB, Parajuli N, Oudit GY. Role of angiotensin-converting enzyme 2 (ACE2) in diabetic cardiovascular complications. *Clin Sci (Lond).* 2014 Apr;126(7):471-82. doi: 10.1042/CS20130344. PMID: 24329564.
 23. -Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, Amadou C, Arnault G, Baudoux F, Bauduceau B, Borot S, Bourgeon-Ghittori M, Bourron O, Boutoille D, Cazenave-Roblot F, Chaumeil C, Cosson E, Coudol S, Darmon P, Disse E, Ducet-Boiffard A, Gaborit B, Joubert M, Kerlan V, Laviolle B, Marchand L, Meyer L, Potier L, Prevost G, Riveline JP, Robert R, Saulnier PJ, Sultan A, Thébaut JF, Thivolet C, Tramunt B, Vazier C, Roussel R, Gautier JF, Gourdy P; CORONADO investigators.. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia* (2020) 63(8):1500–15. doi: 10.1007/s00125-020-05180-x
 24. -Crouse AB, Grimes T, Li P, Might M, Ovalle F, Shalev A. Metformin Use Is Associated With Reduced Mortality in a Diverse Population With COVID-19 and Diabetes. *Front Endocrinol (Lausanne).* 2021 Jan 13;11:600439. doi: 10.3389/fendo.2020.600439. PMID: 33519709; PMCID: PMC7838490.
 25. -Vera IM, Grilo Ruivo MT, Lemos Rocha LF, Marques S, Bhatia SN, Mota MM, Mancio-Silva L. Targeting liver stage malaria with metformin. *JCI Insight.* 2019 Dec 19;4(24):e127441. doi: 10.1172/jci.insight.127441. PMID: 31852843; PMCID: PMC6975259.
 26. -Gedawy A, Al-Salami H, Dass CR. Role of metformin in various pathologies: state-of-the-art microcapsules for improving its pharmacokinetics. *Ther Deliv.* 2020 Nov;11(11):733–753. doi: 10.4155/tde-2020-0102. Epub 2020 Sep 23. PMID: 32967584.
 27. -Liang H., Ding X., Li L., Wang T., Kan Q., Wang L. Association of preadmission metformin use and mortality in patients with sepsis and diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Crit Care.* 2019 Feb 18;23(1):50.
 28. -Xin G, Wei Z, Ji C, Zheng H, Gu J, Ma L, Huang W, Morris-Natschke SL, Yeh JL, Zhang R, Qin C, Wen L, Xing Z, Cao Y, Xia Q, Lu Y, Li K, Niu H, Lee KH, Huang W. Metformin Uniquely Prevents Thrombosis by Inhibiting Platelet Activation and mtDNA Release. *Sci Rep* (2016) 6:36222. 10.1038/srep36222

29. -Scheen AJ. Metformin and COVID-19: From cellular mechanisms to reduced mortality. *Diabetes Metab.* 2020;46(6):423–426. doi:10.1016/j.diabet.2020.07.006

30. -Sharma S, Ray A, Sadasivam B. Metformin in COVID-19: A possible role beyond diabetes. *Diabetes Res Clin Pract.* 2020 Jun;164:108183. doi: 10.1016/j.diabres.2020.108183. Epub 2020 Apr 30. PMID: 32360697; PMCID: PMC7190487.

31. -Singh AK, Singh R. Is metformin ahead in the race as a repurposed host-directed therapy for patients with diabetes and COVID-19? *Diabetes Res Clin Pract.* 2020 Jul;165:108268. doi: 10.1016/j.diabres.2020.108268. Epub 2020 Jun 10. PMID: 32533990; PMCID: PMC7836896.

Tables

Table 1: Descriptive Characteristics of the Patients

Age (years)	<i>Min-Max (Median)</i>	27-88 (60)
	<i>Mean±SD</i>	56.60±12.02
Gender	Female	82 (39.6)
	Male	125 (60.4)
Length of Hospital Stay (days)	<i>Min-Max (Median)</i>	3-55 (11)
	<i>Mean±SD</i>	13.66±8.08
Pneumonia severity	No findings	3 (1.4)
	Atypical	6 (2.9)
	Mild	54 (26.1)
	Moderate	84 (40.6)
	Severe	60 (29.0)
Mortality	Discharged	195 (94.2)
	Exitus	12 (5.8)
Disease course	Moderate	82 (39.6)
	Severe	101 (48.8)
	Critical	24 (11.6)
Drugs used	None	50 (24.2)
	1 drug	56 (27.1)
	2 drugs	33 (15.9)
	≥3 drugs	68 (32.9)
	Metformin	121 (77.1)
	Sulfonylurea	46 (29.3)
	Acarbose	3 (1.9)
	Dpp-4	71 (45.2)
	Pioglitazone	22 (14.0)
	Sgl-2	26 (16.6)
	Insulin	66 (42.0)

Table 2: Distribution of Biochemical Results

	Min-Max (Median)	Mean±SD
HbA1c (%)	5.8-16 (8.6)	9.14±2.31
Glucose (mg/dL)	66-704 (237)	246.11±113.98
Hemoglobin(g/dL)	7.4-16.6 (12.9)	12.85±1.78
Hematocrit(%)	25.3-48.4 (38.7)	38.38±4.62
Leukocytes (10³/uL)	6.1-28950 (7080)	7659.58±3916.84
Lymphocytes (10³/uL)	90-5220 (1140)	1303.94±782.42
Neutrophils (10³/uL)	370-22030 (4990)	5830.63±3526.06
Eosinophils (10³/uL)	0-690 (10)	47.34±108.03
Thrombocytes (10³/uL)	44-954 (216)	231.83±104.14
AST(Aspartate Aminotransferase)	11-205 (33)	43.23±29.35
ALT(Alanine aminotransferase)	8-225 (28)	37.3±32.91
Urea(mg/dL)	15-149 (38)	43.01±20.52
Creatinine (mg/dL)	0.4-5.9 (0.89)	0.96±0.45
LDH(Lactate dehydrogenase)	133-1136 (316)	355.15±149.51
Albumin(g/L)	2.6-5 (3.72)	3.71±0.46
Ferritin(µg/L)	10-3516 (271)	404.29±447.21
Triglycerides (mg/dl)	27-548 (116)	151.08±86.52
CK (Creatin Kinase)	17-3945 (87)	199.43±429.73
Procalcitonin(ng/mL)	0-66 (0.1)	0.98±6.21
CRP (C-reactive protein)	1-418 (92)	106.56±78.55
Fibrinogen(mg/dL)	152-925 (489)	494.06±116.56
PT(Prothrombin time)	10.7-93 (13)	14.12±6.45
APTT(secs)	24.5-100 (35)	36.28±7.56
D-dimer(µg/dL)	0-8.2 (0.32)	0.66±1.18

Table 3: Comparisons according to mortality

		Mortality		
		Discharged	Exitus	<i>p</i>
Age (years)	<i>Min-Max (Median)</i>	27-88 (59)	44-85 (66.5)	<i>a</i>0.051
	<i>Mean±SD</i>	59.20±11.98	66.17±11.22	
Gender	Female	75 (91.5)	7 (8.5)	<i>b</i>0.226
	Male	120 (96.0)	5 (4.0)	
HbA1c	<i>Min-Max (Median)</i>	5.8-16 (8.6)	6.1-14.3 (8.1)	<i>c</i>0.397
	<i>Mean±SD</i>	9.17±2.30	8.68±2.40	
Glucose	<i>Min-Max (Median)</i>	66-704(237)	94-367(257.5)	<i>a</i>0.859
	<i>Mean±SD</i>	246.45±115.45	240.41±90.28	
Drugs used	None	46 (92.0)	4 (8.0)	<i>d</i>0.115
	1 drug	50 (89.3)	6 (10.7)	
	2 drugs	32 (97.0)	1 (3.0)	
	≥3 drugs	67 (98.5)	1 (1.5)	
Metformin	No	31 (86.1)	5 (13.9)	<i>b</i>0.016*
	Yes	118 (97.5)	3 (2.5)	
Sulfonylurea	No	105 (94.6)	6 (5.4)	<i>b</i>1.000
	Yes	44 (95.7)	2 (4.3)	
Acarbose	No	146 (94.8)	8 (5.2)	<i>b</i>1.000
	Yes	3 (100.0)	0 (0.0)	
dpp-4	No	80 (93.0)	6 (7.0)	<i>b</i>0.295
	Yes	69 (97.2)	2 (2.8)	
Pioglitazone	No	127 (94.1)	8 (5.9)	<i>b</i>0.601
	Yes	22 (100.0)	0 (0.0)	
sglt-2	No	124 (94.7)	7 (5.3)	<i>b</i>1.000
	Yes	25 (96.2)	1 (3.8)	
Insulin	No	87 (95.6)	4 (4.4)	<i>b</i>0.721

Yes	62 (93.9)	4 (6.1)
-----	-----------	---------

^aStudent's *t*-test

^bFisher's Exact Test

^cMann Whitney U-test

^dFisher Freeman Halton Test

**p*<0.05

Table 4: Evaluation of the HbA1c values according to the CT findings and disease severity

		HbA1c		
		Min-Max (Median)	Mean±SD	<i>p</i>
Pneumonia severity	• no findings (n=3)	6.5-15.4 (11.5)	11.13±4.46	^e 0.070
	Atypical (n=6)	7.7-14.3 (10.8)	10.77±2.33	
	Mild (n=54)	5.9-16 (9.35)	9.63±2.67	
	Moderate (n=84)	5.8-14.8 (8.45)	9.00±2.12	
	Severe (n=60)	6-14.9 (8.4)	8.64±1.94	
Disease course	Moderate (n=82)	5.9-16 (9)	9.48±2.53	^e 0.392
	Severe (n=101)	5.8-14.8 (8.5)	8.91±2.17	
	Critical (n=24)	6.1-14.3 (8.65)	8.93±2.00	

^eKruskal Wallis Test • not included in the comparison because of the low number of subjects

Table 5: Evaluation of the drugs used according to the disease course

		Disease Course			<i>p</i>
		Moderate	Severe	Critical	
		n (%)	n (%)	n (%)	
Drugs used	None	12 (14.6)	30 (29.7)	8 (33.3)	<i>d</i> _{0.061}
	1 drug	22 (26.8)	25 (24.8)	9 (37.5)	
	2 drugs	13 (15.9)	17 (16.8)	3 (12.5)	
	≥3 drugs	35 (42.7)	29 (28.7)	4 (16.7)	
Metformin	No	17 (24.3)	11 (15.5)	8 (50.0)	<i>f</i> _{0.012*}
	Yes	53 (75.7)	60 (84.5)	8 (50.0)	
Sulfonylurea	No	45 (64.3)	54 (76.1)	12 (75.0)	<i>f</i> _{0.284}
	Yes	25 (35.7)	17 (23.9)	4 (25.0)	
Acarbose	No	69 (98.6)	70 (98.6)	15 (93.8)	<i>d</i> _{0.451}
	Yes	1 (1.4)	1 (1.4)	1 (6.3)	
dpp-4	No	33 (47.1)	44 (62.0)	9 (56.3)	<i>f</i> _{0.208}
	Yes	37 (52.9)	27 (38.0)	7 (43.8)	
Pioglitazone	No	64 (91.4)	57 (80.3)	14 (87.5)	<i>f</i> _{0.160}
	Yes	6 (8.6)	14 (19.7)	2 (12.5)	
sglt-2	No	58 (82.9)	59 (83.1)	14 (87.5)	<i>f</i> _{0.898}
	Yes	12 (17.1)	12 (16.9)	2 (12.5)	
Insulin	No	38 (54.3)	43 (60.6)	10 (62.5)	<i>f</i> _{0.697}
	Yes	32 (45.7)	28 (39.4)	6 (37.5)	

^dFisher Freeman Halton Test

^fPearson Chi-Square Test

**p*<0.05