Original Research Report

METFORMIN EFFECTIVENESS IN REDUCING MORTALITY OF COVID-19 PATIENTS WITH TYPE 2 DIABETES MELLITUS AT A TERTIARY HOSPITAL IN INDONESIA

Yudivaniel Zihono[1], Hany Yusmaini[2*], Uswatun Hasanah[3], Erna Harfiani[2], Md Ikhsan Mokoagow[4], Dicky Budiman[5]

[1]Faculty of Medicine, Universitas Pembangunan Nasional "Veteran" Jakarta, Jakarta, Indonesia
[2]Department of Pharmacology, Faculty of Medicine, Universitas Pembangunan Nasional "Veteran" Jakarta, Jakarta, Indonesia
[3]Department of Molecular Biology, Faculty of Medicine, Universitas Pembangunan Nasional "Veteran" Jakarta, Jakarta, Indonesia
[4]Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, Fatmawati Central General Hospital, Jakarta, Indonesia
[5]Centre for Environmental and Population Health, School of Medicine and Dentistry, Griffith University, Brisbane, Australia

ABSTRACT

COVID-19 patients with comorbidities, such as type 2 diabetes (T2DM), have a higher mortality rate compared to those without any comorbidities. T2DM patients usually receive metformin as their first-line treatment. However, the effectiveness of metformin in reducing mortality rates still requires further analysis. The objective of this study was to analyze the effectiveness of metformin in reducing mortality rates among COVID-19 patients with T2DM. An analytical observational design with a retrospective cohort approach was used in this study. Samples were acquired from hospitalized COVID-19 patients with T2DM medical records at Fatmawati Central General Hospital, Jakarta, Indonesia, from 2020 to 2021. The samples were collected using a purposive sampling technique and analyzed using Chi-square test ($p<0.05$; $RR<1$). This study comprised 137 samples, with 56 of which received metformin and 81 of which did not receive metformin. The mortality rate in the sample group that received metformin was lower (19.6%) compared to the group that was not given the medication (38.3%). The Chi-square test results indicated a statistically significant relationship between metformin treatment and a lower mortality rate among COVID-19-contracted individuals with T2DM ($p=0.020$; $RR=0.513$). Therefore, this study concludes that the administration of metformin reduces mortality among COVID-19 patients with T2DM.

Keywords: Comorbidity; COVID-19; metformin; mortality; type 2 diabetes mellitus (T2DM)

***Correspondence:** Hany Yusmaini, Department of Pharmacology, Faculty of Medicine, Universitas Pembangunan Nasional "Veteran" Jakarta, Jakarta, Indonesia. Email: hany.yusmaini@gmail.com

Article history
●Submitted 5/5/2023 ● Revised 10/7/2023 ● Accepted 12/8/2023 ● Published 10/9/2023

How to cite: Zihono Y, Yusmaini H, Hasanah U, et al (2023). Metformin Effectiveness in Reducing Mortality of Covid-19 Patients with Type 2 Diabetes Mellitus at a Tertiary Hospital in Indonesia. Folia Medica Indonesiana 59 (3), 267-273, https://doi.org/10.20473/fmi.v59i3.46944

pISSN:2355-8393, eISSN: 2599-056x

Highlights:
1. As there is a scarcity of publications on the use of metformin for COVID-19 in Indonesia, the findings of this present study may contribute more insight to the existing body of research and provide data specific to the Southeast Asian population.
2. This study revealed a decreased mortality rate associated with metformin use in diabetic patients with mild to moderate COVID-19 infection.
3. This study suggests that diabetic patients may continue metformin treatment during a COVID-19 infection as the medication has sustained therapeutic effects.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) was initially discovered in Wuhan, China. It is an infectious disease brought on by the SARS-CoV-2 virus (Centers for Disease Control and Prevention 2023). Indonesia has witnessed a substantial number of reported positive cases and a high mortality rate associated with this particular disease. According to a national report in May 2023, the total number of positive cases recorded nationwide was 6,807,513, while the region of Jakarta accounted for 1,408,154 cases. In South Jakarta, a total of 322,317 cases were officially confirmed up until May 2023, with 3,247 fatalities reported (Satgas COVID-19 2022). The presence of comorbidities, such as type 2 diabetes mellitus (T2DM), is one of the factors contributing to the increased mortality rate in COVID-19 patients. According to the preliminary data obtained from Fatmawati Central General Hospital, Jakarta, Indonesia, it was found that 16 patients who were diagnosed with COVID-19 also had T2DM. Furthermore, the data reported that 68.8% of these patients were deceased (Kshanti et al. 2020, Harbuwono et al. 2022). COVID-19 patients with T2DM reportedly accounted for 36.4% of the positive cases in Jakarta, according to the data on 738 cases. The mortality rate among these patients was reported to be 11.9% (Satgas COVID-19 2022).

Metformin is typically prescribed as a first-line treatment for individuals diagnosed with T2DM due to its ability to lower blood glucose levels. This medication is a therapeutic agent for hyperglycemia by enhancing insulin sensitivity in the body. The mechanism to increase body sensitivity toward insulin is possible through the phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) and the translocation of glucose transporter type 4 (GLUT4), thus facilitating an increased uptake of glucose into the cells. In addition, metformin has an anti-inflammatory effect that works by suppressing the release of cytokines and chemokines, such as interleukin 6 (IL-6), interleukin 1 beta (IL-1β), and tumor necrosis factor beta (TNF-β). This suggests that metformin may have a potential therapeutic advantage that suppresses COVID-19 inflammation in T2DM patients who have contracted the infectious disease (Kamyshnyi et al. 2021).

Previous studies have investigated the effectiveness of metformin in COVID-19 patients with T2DM. A study found a lower mortality rate in patients who received metformin (3%) than those who did not (11%). The study included 328 COVID-19 patients with T2DM, with a categorization of severe (31.4%) and non-severe COVID-19 (68.6%) (Jiang et al. 2021). A separate study with 6,256 samples also yielded comparable findings in female patients (HR=0.785; CI=0.650–0.951; p=0.015). However, no significant association was observed in male patients (HR 0.967; CI 0.82-1.14; p = 0.871) (Bramante et al. 2021). In another study with a sample size of 1,213 and a COVID-19 categorization of mild and severe, it was found that the administration of high-dose metformin increased acidosis incidence. Nevertheless, the study did not find any significant effect on patient mortality (adjusted HR=0.87; 95% CI=0.36–2.12; p=0.757) (Cheng et al. 2020). The aforementioned studies have provided evidence about the effectiveness and effects of metformin in COVID-19 patients with T2DM.

The side effects of metformin pose a challenge for healthcare professionals to evaluate its potential benefits and risks. This underlines the need for further research into the effectiveness of metformin, particularly in reducing mortality rates among COVID-19 patients with T2DM. Such studies, however, remain scarce in Indonesia. The objective of this study was to assess the effectiveness of metformin in lowering mortality among COVID-19 patients with T2DM at Fatmawati Central General Hospital, Jakarta, Indonesia. The findings of this study may be helpful in providing valuable insights into the improved management of COVID-19 and T2DM.

MATERIALS AND METHODS

This study employed an analytical observational design with a retrospective cohort method. Data were collected from the medical records of 137 COVID-19 patients with T2DM who were hospitalized at Fatmawati Central General Hospital between 2020 and 2021. Fatmawati Central General Hospital is located in South Jakarta, Indonesia. The sample size was determined using a two-population proportion hypothesis test, resulting in a minimum requirement of 108 samples. This study used a purposive sampling technique. The inclusion criteria were T2DM patients who were diagnosed with mild to moderate COVID-19 and within the age range of 20–85 years. The patients included in this study were either receiving metformin as monotherapy, as part of a combination therapy, or were not receiving metformin treatment at all. The clinical classification of COVID-19 severity was determined according to the COVID-19 Management Guidelines (Burhan et al. 2022). Patients with comorbidities other than T2DM (e.g., cardio-vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, and chronic kidney disease) and immunocompromised patients were excluded from this study.

The independent variable was the administration of metformin, while the dependent variable was patient

mortality. The data collected in this study comprised several patient characteristics, such as gender, age, clinical classification of COVID-19 severity, body mass index (BMI), as well as the administration of metformin and other medications. The data were then documented and organized with Microsoft Excel for Windows, version 16.0 (Microsoft Inc., Redmont, WA, USA). The statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA). The frequency data were presented using tables. The Chi-square test was used in the analysis of the relationship between the dependent and independent variables. A significance level of $p<0.05$ indicated a significant relationship (Sutriyawan 2021). This study obtained permission from the Research Ethics Committee of the Faculty of Medicine, Universitas Pembangunan Nasional "Veteran" Jakarta, Jakarta, Indonesia, with approval letter No. 76/IV/2023/ KEPK on 11/4/2023.

RESULTS

After applying the predetermined inclusion and exclusion criteria, a total of 202 patient data sets were collected from medical records. Additional screening was conducted, resulting in the exclusion of 65 data sets due to incomplete information. A total of 137 data sets were deemed eligible for analysis.

Table 1 displays the characteristics of T2DM patients who were diagnosed with COVID-19. The majority of the patients exhibited characteristics such as advanced age, male gender, moderate symptoms, and obesity. There were more patients who did not receive metformin treatment compared to those who did, showing that the non-metformin group accounted for the majority of total samples. The patients' characteristics showed no statistically significant difference between the metformin and non-metformin groups ($p>0.05$).

Among the 137 COVID-19 patients with T2DM in this study, only 56 individuals received metformin treatment. Table 2 shows the distribution of metformin administration among these patients. Only six patients received metformin as monotherapy, while the remaining patients received the medication as part of combination therapy.

Table 3 categorizes the administration of medications other than metformin. The majority of the patients were prescribed antidiabetic drugs, with insulin being the most commonly used medication. The results showed that there were no statistically significant differences between groups in terms of the administration of medications other than metformin ($p>0.05$).

Table 1. Characteristics of patients in the metformin and non-metformin groups.

Characteristics	Frequency [n (%)]		%	p
	Metformin group [n=56 (40.9%)]	Non-metformin group [n=81 (59.1%)]		
Age				>0.05
20–39 y.o.	6 (10.7)	10 (12.3)	11.7	
40–49 y.o.	8 (14.3)	15 (18.5)	16.8	
50–59 y.o.	15 (26.8)	30 (37.0)	32.8	
60–69 y.o.	22 (39.3)	20 (24.7)	30.7	
70–79 y.o.	4 (7.1)	5 (6.2)	6.6	
≥80 y.o.	1 (1.8)	1 (1.2)	1.5	
Sex				>0.05
Male	30 (53.6)	40 (49.4)	51.1	
Female	26 (46.4)	41 (50.6)	48.9	
COVID-19 severity				>0.05
Mild	21 (37.5)	37 (45.7)	42.3	
Moderate	35 (62.5)	44 (54.3)	57.7	
BMI				>0.05
Underweight	3 (5.4)	1 (1.2)	2.9	
Normal	17 (30.4)	26 (32.1)	31.4	
Overweight	10 (17.9)	20 (24.7)	21.9	
Obesity	26 (46.4)	34 (42.0)	43.8	

Table 2. Distribution of metformin administration as monotherapy and as part of combination therapy.

Category	Frequency [n (%)] [n=56 (40.9%)]	%
Monotherapy	6 (10.7)	4.4
Part of combination therapy	50 (89.3)	36.5

Table 3. Distribution of the administration of medications other than metformin.

Characteristics	Frequency [n (%)]		%	p
	Metformin group [n=56 (40.9%)]	Non-metformin group [n=81 (59.1%)]		
Antidiabetics				>0.05
Thiazolidinedione	0 (0.0)	1 (100.0)	0.7	
DPP-4 inhibitor	0 (0.0)	1 (100.0)	0.7	
Sulfonylurea	7 (30.4)	16 (69.6)	16.8	
α-glucosidase inhibitor	1 (33.3%)	2 (66.7)	2.2	
Insulin	48 (42.1)	66 (57.9)	83.2	
Antiviral	52 (43.0)	69 (57.0)	88.3	> 0.05
Antibiotic	53 (41.1)	76 (58.9)	94.2	> 0.05
Anticoagulant	42 (40.8)	61 (59.2)	75.2	> 0.05
Antifungal	4 (25.0)	12 (75.0)	11.7	> 0.05
Glucocorticoid	36 (45.6)	43 (54.4)	57.7	> 0.05

Notes: DPP-4=Dipeptidyl peptidase-4.

Table 4 presents the distribution of mortality and survival among the total patients in this study. Among the 137 COVID-19 patients with T2DM, a total of 42 patients (30.7%) succumbed to the disease. The majority of the patients, comprising 95 individuals (69.3%), survived following the COVID-19 infection.

Table 4. Distribution of patient mortality and survival.

Category	Frequency (n)	%
Mortality	42	30.7
Survival	95	69.3

Table 5 displays the results of the Chi-square test. The analysis was performed to assess the correlation between metformin administration and patient mortality. The results demonstrated a statistically significant correlation between the administration of metformin and a lower mortality rate among COVID-19 patients with T2DM ($p<0.005$; $RR<1.000$).

Table 5. Results of the Chi-square test of metformin administration and patient mortality.

Groups	Mortality [n (%)]	Survival [n (%)]	p	RR (95% CI)
Metformin	11 (19.6)	45 (80.4)	0.020	0.513 (0.282–0.933)
Non-metformin	21 (38.3)	50 (61.7)		

Notes: RR=Risk ratio.

DISCUSSION

The age grouping used in this study adhered to the same categorization as outlined in the study conducted by Woolcott & Castilla-Bancayán (2021). Patients under the age of 20 were excluded from this study because of the low prevalence of T2DM within this particular age group. The results of this study showed that the majority of the COVID-19 patients with T2DM were concentrated in the age group of 50–59 years (32.8%). According to a study conducted by El Chakhtoura et al. (2017), aging influences the decrease in immune cell recruitment functionality. This particular factor may lead to a higher susceptibility to developing diseases among older adults.

This study showed that there was a higher proportion of male patients in comparison to female patients. This is consistent with the study conducted by Luo et al. (2020), in which the majority of COVID-19 patients with T2DM were male (55.1%). This occurrence could potentially be related to the different behavioral patterns exhibited by men and women. A previous study revealed that women demonstrated a higher prevalence of hygiene habits and adopted healthier lifestyles compared to men. It is possible that this could make men more susceptible to infections (Bwire 2020).

The clinical categorization of the COVID-19 patients in this study showed that the majority of them exhibited moderate symptoms. Yitao et al. (2021) conducted a study that revealed a comparable finding, wherein the prevalence of moderate-severity cases was 12.2% among COVID-19 patients with T2DM. This study reported a higher number of patients with a moderate clinical classification of COVID-19 since Fatmawati Central General Hospital served as a referral center for COVID-19 cases during the pandemic.

The present investigation revealed a high prevalence of obesity among the patient population. Individuals who have diabetes mellitus and obesity have a 4.5 times greater risk of hospitalization compared to those without both conditions Giorgino et al. (2021). According to Holly et al. (2020), COVID-19 patients who have T2DM and obesity commonly experience impairments in immune system functioning. These impairments include disruptions in the activity of T lymphocytes and natural killer cells, which subsequently lead to the development of more severe clinical manifestations.

Most of the patients in this study did not receive metformin treatment. This is consistent with the study by Jiang et al. (2021), who showed that most COVID-19 patients with T2DM did not receive metformin (69.5%). In addition to its immunomodulatory effects, metformin has anti-inflammatory effects through the suppression of cytokines such as IL-6, IL-1β, and TNF-β. Metformin is the first line of T2DM treatment because it can reduce blood glucose levels by phosphorylating AMPK and translocating GLUT4, which can enhance the uptake of glucose into the cells. This medication is administered to T2DM patients who suffer from infections. However, COVID-19 patients generally experience gastrointestinal disorders such as nausea, vomiting, and diarrhea. These manifestations are similar to the adverse effects associated with metformin administration. Therefore, it is imperative to carefully evaluate the patient's state before administering metformin to prevent the onset of worsening symptoms (Groff et al. 2021). This observation may clarify the disparity in the number of patients between the metformin and non-metformin groups.

Insulin was the most widely used antidiabetic treatment in this study. Luo et al. (2020) observed a similar finding among COVID-19 patients with T2DM. In the study, 53.7% of the patients received insulin therapy. Insulin doses can be modified quickly to provide rapid relief from hyperglycemic conditions. Therefore, insulin is frequently used in hospitals for the management of diabetes mellitus (Inzucchi 2023). Other medications used in this study were antivirals, antibiotics, anticoagulants, antifungals, and glucocorticoids. SARS-CoV-2 is

the viral pathogen responsible for the COVID-19 infection. Thus, antiviral therapy is the most optimal approach for its treatment. In a recent trial, antiviral medications were administered to 89.9% of the total samples (Wang et al. 2020). It is worth noting that COVID-19 patients may also receive antibiotic treatment. Viral infections are commonly accompanied by bacterial co-infections (Kristanti et al. 2022). According to the research conducted by Wang et al. (2021), a significant proportion of COVID-19 patients, specifically 98%, received antibiotic treatment. In addition, COVID-19 patients with T2DM frequently experience hyper-coagulation, which consequently requires the administration of anticoagulant medications. According to prior research, 30.7% of diabetic patients diagnosed with COVID-19 received anticoagulants (Luo et al. 2020, Carfora et al. 2021). Diabetes is a risk factor for the development of fungal infections. Meanwhile, COVID-19 increases the susceptibility to fungal infections through endothelial dysfunction (John et al. 2021). In the study by Zhang et al. (2020), it was shown that 12.2% of patients required antifungal medication. The study additionally revealed that 41% of patients received glucocorticoid therapy. Glucocorticoids play a substantial role in COVID-19 treatment due to their anti-inflammatory effects. However, glucocorticoid administration may cause hyperglycemia, so periodic monitoring is necessary (Alexaki & Henneicke 2021).

This study revealed that the majority of the patients survived. Similar results were observed in a recent study, with a survival rate of 57.7% and a mortality rate of 42.3% among the patients (Mirani et al. 2020). Conversely, the study by Harbuwono et al. (2022) discovered that COVID-19 patients with T2DM had a higher mortality rate (21.3%) compared to those without comorbidities (2.8%). Diabetic patients generally experience chronic inflammation due to their hyperglycemic condition. They may exhibit an increased inflammatory response when infected with SARS-CoV-2 (Kamyshnyi et al. 2021). COVID-19 patients with T2DM can notice improved clinical symptoms when their blood glucose levels are properly controlled. However, the researchers did not record the blood glucose levels of the subjects during the course of this study. Future research is required to validate the hypothesis regarding the relationship between blood glucose regulation and patient mortality.

The Chi-square test in this study revealed a significant relationship between a reduced number of fatalities and metformin treatment among COVID-19 patients with T2DM. In a previous study, a relationship was found between metformin therapy and a mortality reduction among the research subjects (p=0.01) (Luo et al. 2020). Several other studies have reported similar findings regarding metformin administration and patient mortality. An association between metformin treatment and mortality rate was demonstrated among the patients of a study (OR=0.64, 95% CI=0.51–0.79) (Yang et al. 2021). Furthermore, the study by Lally et al. (2021) concluded that metformin administration to COVID-19 patients with T2DM resulted in a reduced mortality rate over a 30-day period. Metformin can provide anti-inflammatory effects by suppressing nuclear factor kappa B (NF-κB) signaling. NF-κB functions to express cytokines that can activate the inflammatory response. Through the suppression of NF-κB activity, the patient's body will have a milder inflammation response, resulting in the alleviation of symptoms. Metformin also acts as an immunomodulator by promoting the production of M2 macrophages, regulatory T cells, and cytotoxic T lymphocytes (CD8+ memory T cells). The immunomodulatory action of metformin in COVID-19 patients with T2DM may aid the immune response against the SARS-CoV-2 virus. Metformin has been observed to enhance the activation and phosphorylation of AMPK, which can stabilize angiotensin-converting enzyme 2 (ACE2) receptors by preventing the degradation of proteasomes. A stable structure of the ACE2 receptor may potentially lower the probability of the SARS-CoV-2 spike protein binding to it (Kamyshnyi et al. 2021).

The study demonstrated a significant relationship between metformin administration and reduced mortality rates among COVID-19 patients with T2DM. However, it was also necessary to conduct a comparison between metformin and other medications used for the treatment of diabetes. Prior research has found an association between the administration of insulin and higher mortality rates among COVID-19 patients with T2DM. Sulfonylurea monotherapy was shown to have inconclusive effects, while a combination therapy with metformin showed promising results in lowering mortality (Kan et al. 2021, Ouchi et al. 2022). The effectiveness of monotherapy with α-glucosidase inhibitors yielded ambiguous results. However, a combination therapy with metformin demonstrated more favorable outcomes (Li et al. 2022, Nguyen et al. 2022). The findings of a prior study revealed a lack of correlation between thiazolidinedione administration and patient mortality. Meanwhile, the administration of DPP4-inhibitors produced inconclusive results either in monotherapy or combination therapy, especially with metformin (Chen et al. 2022). Overall, metformin surpassed other diabetes treatments in lowering the mortality rate of COVID-19 patients with T2DM.

Strength and limitations

This study provides information regarding the use of

metformin treatment in reducing the mortality rate among COVID-19 patients with T2DM. However, further research in Indonesia is necessary given the scarcity of published studies on this subject matter. Further studies need to evaluate blood glucose and HbA1c levels in correlation with patient mortality, variables that were not assessed in this study. Furthermore, insulin resistance is important to explore in future studies, considering that the use of insulin is high among COVID-19 patients with T2DM.

CONCLUSION

Metformin, as a first-line treatment for hyperglycemia, is related to decreased mortality rates of COVID-19 patients with T2DM. The administration of metformin is beneficial for COVID-19 patients with T2DM who are at a higher risk of mortality because of their comorbidity. A combination therapy using metformin and other medications continues to result in a notable decrease in mortality rates among COVID-19 patients with T2DM.

Acknowledgment

The authors would like to thank Fatmawati Central General Hospital, Jakarta, Indonesia, as well as to all supervisors who provided valuable assistance during the data collection process.

Conflict of interest

None.

Ethical consideration

The study was ethically approved on 11/4/2023 by the Research Ethics Committee of the Faculty of Medicine, Universitas Pembangunan Nasional "Veteran" Jakarta, Jakarta, Indonesia, with approval letter No. 76/IV/2023/KEPK.

Funding disclosure

None.

Author contribution

YZ contributed to the conception and design, analysis and interpretation of the data, drafting of the article, and statistical expertise. HY, UH, EH, and DB contributed to the critical revision of the article for important intellectual content, final approval of the article, and statistical expertise. MIM contributed to the critical revision of the article for important intellectual content, final approval of the article, provision of study materials, and statistical expertise.

REFERENCES

Alexaki VI, Henneicke H (2021). The role of glucocorticoids in the management of COVID-19. Hormone and Metabolic Research 53**,** 9–15. doi: 10.1055/a-1300-2550.

Bramante CT, Ingraham NE, Murray TA, et al (2021). Metformin and risk of mortality in patients hospitalised with COVID-19: A retrospective cohort analysis. The Lancet Healthy Longevity 2**,** e34–41. doi: 10.1016/S2666-7568(20)30033-7.

Burhan E, Susanto AD, Isbaniah F, et al (2022). Pedoman tatalaksana COVID-19 edisi 4, 4th edn. Jakarta. Available at: https://www.slideshare.net/CIkumparan/buku-tatalaksana-covid19-5-op-edisi-4-jan-2022.

Bwire GM (2020). Coronavirus: Why men are more vulnerable to COVID-19 than women? SN Comprehensive Clinical Medicine 2**,** 874–876. doi: 10.1007/s42399-020-00341-w.

Carfora V, Spiniello G, Ricciolino R, et al (2021). Anticoagulant treatment in COVID-19: A narrative review. Journal of Thrombosis and Thrombolysis 51**,** 642–648. doi: 10.1007/s11239-020-02242-0.

Centers for Disease Control and Prevention (2023). About COVID-19. CDC. Available at: https://www.cdc.gov/coronavirus/2019-ncov/your-health/about-covid-19.html#:~:text=COVID-19 most often causes,some people become severely ill.

El Chakhtoura NG, Bonomo RA, Jump RLP (2017). Influence of aging and environment on presentation of infection in older adults. Infectious Disease Clinics of North America 31**,** 593–608. doi: 10.1016/j.idc.2017.07.017.

Chen Y, Lv X, Lin S, et al (2022). The association between antidiabetic agents and clinical outcomes of COVID-19 patients with diabetes: A bayesian network meta-analysis. Frontiers in Endocrinology (Lausanne). doi: 10.3389/fendo.2022.895458.

Cheng X, Liu Y-M, Li H, et al (2020). Metformin is associated with higher incidence of acidosis, but not mortality, in individuals with COVID-19 and pre-existing type 2 diabetes. Cell Metabolism 32**,** 537-547.e3. doi: 10.1016/j.cmet.2020.08.013.

Giorgino F, Bhana S, Czupryniak L, et al (2021). Management of patients with diabetes and obesity in the COVID-19 era: Experiences and learnings from South and East Europe, the Middle East, and Africa. Diabetes Research and Clinical Practice 172**,** 108617. doi: 10.1016/j.diabres.2020.108617.

Groff A, Kavanaugh M, Ramgobin D, et al (2021). Gastrointestinal manifestations of COVID-19: A review of what we know. Ochsner Journal 21**,** 177–180. doi: 10.31486/toj.20.0086.

Harbuwono DS, Handayani DOTL, Wahyuningsih ES, et al (2022). Impact of diabetes mellitus on COVID-19 clinical symptoms and mortality: Jakarta's COVID-19 epidemiological registry.

Primary Care Diabetes 16, 65–68. doi: 10.1016/j.pcd.2021.11.002.

Holly JMP, Biernacka K, Maskell N, et al (2020). Obesity, diabetes and COVID-19: An infectious disease spreading from the east collides with the consequences of an unhealthy western lifestyle. Frontiers in Endocrinology (Lausanne). doi: 10.3389/fendo.2020.582870.

Inzucchi SE (2023). Management of diabetes mellitus in hospitalized patients. UpToDate. Available at: https://www.uptodate.com/contents/management-of-diabetes-mellitus-in-hospitalized-patients#H9.

Jiang N, Chen Z, Liu L, et al (2021). Association of metformin with mortality or ARDS in patients with COVID-19 and type 2 diabetes: A retrospective cohort study. Diabetes Research and Clinical Practice 173, 108619. doi: 10.1016/j.diabres.2020.108619.

John TM, Jacob CN, Kontoyiannis DP (2021). When uncontrolled diabetes mellitus and severe COVID-19 converge: The perfect storm for mucormycosis. Journal of Fungi 7, 298. doi: 10.3390/jof7040298.

Kamyshnyi O, Matskevych V, Lenchuk T, et al (2021). Metformin to decrease COVID-19 severity and mortality: Molecular mechanisms and therapeutic potential. Biomedicine & Pharmacotherapy 144, 112230. doi: 10.1016/j.biopha.2021.112230.

Kan C, Zhang Y, Han F, et al. (2021). Mortality risk of antidiabetic agents for type 2 diabetes with COVID-19: A systematic review and meta-analysis. Frontiers in Endocrinology (Lausanne). doi: 10.3389/fendo.2021.708494.

Kristanti W, Yulia R, Herawati F (2022). Analysis of antibiotic use in COVID-19 patients at a hospital in Sidoarjo. Jurnal Farmasi dan Ilmu Kefarmasian Indonesia 9, 200–208. doi: 10.20473/jfiki.v9i22022.200-208.

Kshanti IA, Aji G, Epriliawati M, et al (2020). Clinical presentation and outcome of COVID-19 infection in Type 2 Diabetes Mellitus: A preliminary data from a tertiary hospital in Jakarta during the early days of the pandemic. Bali Medical Journal 9, 787–793. doi: 10.15562/bmj.v9i3.1969.

Lally MA, Tsoukas P, Halladay CW, et al (2021). Metformin is associated with decreased 30-day mortality among nursing home residents infected with SARS-CoV2. Journal of the American Medical Directors Association 22, 193–198. doi: 10.1016/j.jamda.2020.10.031.

Li J, Wei Q, McCowen KC, et al (2022). Inpatient use of metformin and acarbose is associated with reduced mortality of COVID-19 patients with type 2 diabetes mellitus. Endocrinology, Diabetes & Metabolism. doi: 10.1002/edm2.301.

Luo P, Qiu L, Liu Y, et al (2020). Metformin treatment was associated with decreased mortality in COVID-19 patients with diabetes in a retrospective analysis. The American Journal of Tropical Medicine and Hygiene 103, 69–72. doi: 10.4269/ajtmh.20-0375.

Mirani M, Favacchio G, Carrone F, et al (2020). Impact of comorbidities and glycemia at admission and dipeptidyl peptidase 4 inhibitors in patients with Type 2 Diabetes With COVID-19: A case series from an Academic Hospital in Lombardy, Italy. Diabetes Care 43, 3042–3049. doi: 10.2337/dc20-1340.

Nguyen NN, Ho DS, Nguyen HS, et al (2022). Preadmission use of antidiabetic medications and mortality among patients with COVID-19 having type 2 diabetes: A meta-analysis. Metabolism 131, 155196. doi: 10.1016/j.metabol.2022.155196.

Ouchi D, Vilaplana-Carnerero C, de Dios V, et al (2022). Antidiabetic treatment and COVID-19 Outcomes: A population-based cohort study in primary health care in Catalonia during the first wave of the pandemic. Primary Care Diabetes 16, 753–759. doi: 10.1016/j.pcd.2022.10.001.

Satgas COVID-19 (2022). Peta sebaran Covid-19. Available at: https://covid19.go.id/peta-sebaran.

Sutriyawan A (2021). Metodologi penelitian kedokteran dan kesehatan (dilengkapi tuntunan membuat proposal penelitian). Refika Aditama, Bandung.

Wang L, Amin AK, Khanna P, et al (2021). An observational cohort study of bacterial co-infection and implications for empirical antibiotic therapy in patients presenting with COVID-19 to hospitals in North West London. Journal of Antimicrobial Chemotherapy 76, 796–803. doi: 10.1093/jac/dkaa475.

Woolcott OO, Castilla-Bancayán JP (2021). The effect of age on the association between diabetes and mortality in adult patients with COVID-19 in Mexico. Scientific Reports 11, 8386. doi: 10.1038/s41598-021-88014-z.

Yang W, Sun X, Zhang J, et al (2021). The effect of metformin on mortality and severity in COVID-19 patients with diabetes mellitus. Diabetes Research and Clinical Practice 178, 108977. doi: 10.1016/j.diabres.2021.108977.

Yitao Z, Mu C, Ling Z, et al (2021). Predictors of clinical deterioration in non-severe patients with COVID-19: A retrospective cohort study. Current Medical Research and Opinion 37, 385–391. doi: 10.1080/03007995.2021.1876005.

Zhang J, Kong W, Xia P, et al (2020). Impaired fasting glucose and diabetes are related to higher risks of complications and mortality among patients with Coronavirus Disease 2019. Frontiers in Endocrinology (Lausanne). doi: 10.3389/fendo.2020.00525.