

Study of Potential Drug Interactions in COVID-19 Patients with Comorbid Type 2 Diabetes Mellitus at The General Hospital in South Tangerang City, Period 2021

Nurmeilis^{1*}, Yusroh Umami¹, Nurhaida M², Delila Eliza¹

¹. Department of Pharmacy, Faculty of Health Sciences, UIN Syarif Hidayatullah Jakarta, Jl. Kertamukti No.5 Ciputat, South Tangerang Banten 15419, Indonesia

². General Hospital in South Tangerang City, Jl. Pajajaran No. 101, Pamulang, South Tangerang Selatan, Banten 15417, Indonesia

*Corresponding author: nurmeilis@uinjkt.ac.id

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Abstract: Diabetes mellitus is one of the common comorbidities found in COVID-19 patients. The use of large amounts of medication (polypharmacy) in COVID-19 patients with comorbid diabetes mellitus can increase the possibility of drug interactions. The study aimed to determine the potential drug-drug interactions and its relationship with clinical outcomes in COVID-19 patients with comorbid type 2 diabetes mellitus at the General Hospital in South Tangerang City. The study was a retrospective study conducted in the hospital by using patients' medical records from January-December 2021. Potential drug-drug interactions were analyzed by using the software, Medscape, and Drugs.com. The 97 patients met the inclusion and exclusion criteria. The results of the study were found in 40 patients who experience drug interactions with COVID-19 drugs and antidiabetics (58.2%), the majority of them are in moderate severity degree (78.5%), major severity degree (21.5%), with pharmacodynamic mechanism (100%). There is no significant relationship between drug interactions and clinical outcomes of patients ($P > 0.05$). The interactions found were all pharmacodynamic, although there was no significant relationship to clinical outcomes, therapeutic monitoring was still required.

Keywords: clinical outcome, covid-19, diabetes mellitus, drug interaction

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1. INTRODUCTION

In early 2020, the world was informed of a new variant of the coronavirus, SARS-CoV-2. The results showed that a new type of betacoronavirus infection, named SARS-CoV-2, was discovered at the end of December 2019 in Wuhan, China. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) attacks the respiratory system in humans, especially the part of the cells lining the alveoli, which are attacked by a new virus known as COVID-19 (Kementerian Kesehatan Republik Indonesia, 2020). Patients with COVID-19 have various comorbidities such as hypertension 49.9%, diabetes mellitus 36.6%, and heart disease 16.8% (Satgas COVID-19, 2021). COVID-19 patients with comorbid diabetes mellitus are in second place in Indonesia. From the data, it can be concluded that during the pandemic, many diabetics. Diabetes mellitus is one of the factors that can cause an increase in the severity of COVID-19. This happens because of the body's immune system dysfunction in patients with diabetes mellitus, especially in patients whose blood sugar cannot be controlled. Innate immunity in diabetes mellitus patients is affected by hyperglycemia by interfering with the production of type I interferon which has antiviral properties (Singh et al., 2020).

Treatments used by patients with COVID-19 and diabetes mellitus are antivirals such as favipiravir or remdesivir; multivitamins such as vitamin C and vitamin D, corticosteroids such as methylprednisolone and anticoagulants such as heparin and anti-diabetic insulin, metformin, and other anti-diabetic groups (Kementerian Kesehatan Republik Indonesia, 2021). Treatment of COVID-19 patients who have comorbid diabetes mellitus raises the potential for polypharmacy. Polypharmacy is the use of drugs

simultaneously in large quantities that are not by the patient's condition or the expected clinical effect, in which polypharmacy will increase the risk of drug interactions. Drug interaction is an event that occurs when the pharmacological effect of a drug is altered by the presence of other drugs in the same metabolism (Thanacoody, 2019). One of the hospitals that handle COVID-19 cases is the South Tangerang City Hospital. based on a field survey at this General Hospital, 175 COVID-19 patients have comorbid diabetes mellitus in 2021. Given that drug interactions are a very high-risk factor, and diabetes mellitus is also a risk factor that can increase the severity and death in COVID-19 patients, research on related matters is still a small number of studies. Thus, this research is very important to do which aims to identify potential drug interactions given to COVID-19 patients with comorbid diabetes mellitus type 2 so that later on improving the quality of life of patients and can prevent the occurrence of unwanted events related to treatment

2. METHODS

2.1 Research Design

This retrospective study conducted in a cross-sectional study design using secondary data in the form of medical records. The aim of study was to identify and analyze drug interactions in COVID-19 patients with comorbid type 2 diabetes mellitus at the South Tangerang City General Hospital in 2021. The tool used in this study was drugs.com and Medscape to analyze potential drug interactions. Drug interactions were differentiated based on the severity of undesirable effects, categorized into major, moderate and minor, while drug interactions based on their mechanisms were differentiated into pharmacokinetic and pharmacodynamic)

2.2 Sample

Inclusion criteria for this study were inpatients diagnosed COVID-19 with comorbid diabetes mellitus in 2021. Patients with incomplete medical records were excluded. Sampling was conducted using the total sampling method. The sample that met the inclusion and exclusion criteria was 97 patients.

2.3. Ethical Clearance

This research has passed the ethics review at the Faculty of Health Sciences UIN Syarif Hidayatullah Jakarta with the letter No. UN.01/F.10/KP.01.1/KE.SP/03.08.011/2022.

2.4. Data Analysis

Data analysis was performed using statistical tests using IBM SPSS Statistics, consisting of univariate and bivariate analyses. Univariate analysis was used to observe the distribution of patient characteristics, the percentage of potential drug interactions, and the percentage distribution of drug interaction categories based on the severity and mechanism of drug interactions. Furthermore, bivariate analysis was performed to analyze the correlation factors between potential drug interactions and clinical outcomes using the chi-square analysis. The analysis results were declared significant if the p-value <0.05.

3. RESULTS AND DISCUSSION

3.1 Characteristic of COVID-19 Patients with Comorbid Type 2 Diabetes Mellitus

Characteristics of COVID-19 patients with comorbid diabetes mellitus in this study include age, gender, and several drug use. The number of COVID-19 patients with comorbid type 2 diabetes mellitus in the hospitalization of South Tangerang City Hospital in 2021 who met the inclusion criteria was 97 patients. The gender of COVID-19 patients with comorbid diabetes mellitus out of 97 patients was dominated by women with 54 people (55.7%) compared to men with 43 people (44.3%). The results of this study

are inconsistent with some research results where the research conducted by Maulidia et al. (2021), explains that men are more dominant. It was supported by another research explained that men have more ACE-2 receptors (targets for initiation of SARS-CoV-2 to enter the target cell) than woman (Lipsky & Hung, 2020). Men have only 1 X chromosome as a regulator in the immune system, especially the adaptive immune response, while women have 2 X chromosomes (Schurz et al., 2019).

In this study, the results were obtained that the female sex was more infected with COVID-19 with comorbid Diabetes Mellitus. This is because the prevalence of Diabetes Mellitus in Indonesia itself occurs more in the female sex with a percentage of 32.7%. This finding was in accordance with Riset Kesehatan Dasar 2018 report that the prevalence of diabetes mellitus sufferers in Indonesia was higher among women than men (Badan Penelitian dan Pengembangan Kesehatan, 2019). Furthermore, gender differences in diabetes prevalence are inversely related to reproductive life stage. More men suffer from diabetes before puberty, while more women suffer from diabetes after menopause and later in life (Ciarambino et al., 2022). In this study, the majority of patients were over 55 years of age (Table 1).

Table 1. Characteristics of COVID-19 Patients Based on Gender, Age, and Number of Drug Use in Hospitalizations of South Tangerang Hospital in 2021

No	Characteristic	Amount (n=97)	Percentage (%)
1	Gender		
	a. Men	43	44,3
	b. Women	54	55,7
2	Age (Years)		
	a. <25	0	0
	b. 25-34	4	4,1
	c. 35-44	13	13,4
	d. 45-54	31	32,0
	e. 55-64	36	37,1
	f. ≥ 65	13	13,4
3	Number of drugs administered to patients		
	a. < 5 drugs	0	0
	b. ≥ 5 drugs	97	100

Characteristics in terms of age, the youngest age in this study is <25 years and the oldest age is ≥65 years. explained that for the age category of COVID-19 sufferers with comorbid type 2 diabetes mellitus, the most dominant occurred at the age of 55-64 years (37.1%). This was in line with Haryati's research which explains that patients between the age of 55-64 years are more likely to be exposed to COVID-19 (Haryati et al., 2021). This is because patients at the age of 55 years have long-term health problems or comorbidities and risk-reducing natural immunity in patients (Hikmawati & Setiyabudi, 2020). The aging process can weaken the function of T cells and B cells and excessive production of pro-inflammatory cytokines will lead to control of viral replication and a continuing proinflammatory response, consequently, in old age, it can lead to poor conditions if infected with SARS-CoV-2 (Smits et al., 2010).

The results of this study indicate that all research subjects utilized ≥5 drugs. The use of more or the same 5 kinds of drugs simultaneously daily is called polypharmaceutical. Polypharmacy has an association with increasing the risk of DRPs (drug-related problems) and clinical outcomes that can harm patients. In previous studies, it was explained that the potential factors of DRPs (drug-related problems) have a relationship between polypharmacy and the incidence of drug interactions. The risk of drug interactions can consistently be seen to increase exponentially from linearly to the amount of medication consumed by patients (Koh et al., 2005).

In recent studies, it was explained that polypharmacy is associated with clinical outcomes that can be detrimental to COVID-19 patients, and from clinical results it is reported that drug interactions can increase the risk of COVID-19 infection, aggravating COVID-19 patients and death. Thus, for COVID19 patients, it is necessary to make dose adjustments (Iloanusi et al., 2021)

3.2 Prevalance of COVID-19 Potential Drug Interactions

The results of the analysis Prevalence of Overall Drug Interactions in Any COVID-19 Patient with Comorbid Diabetes Mellitus Type 2 in Inpatient Hospital South Tangerang City Year 2021 in this study obtained results from 97 patients, there were 67 (69.1%) patients who experienced drug interactions and 30 (30.9%) patients who did not experience drug interactions.

Table 2. Prevalence of COVID-19 Potential Drug Interactions with Antidiabetics in COVID-19 Patients with Comorbid Diabetes Mellitus Type 2 in Patient Hospitals of South Tangerang City Hospital in 2021

No	Interaction of COVID-19 drugs with Antidiabetic	Frequency	Percentage (%)
1.	Drug Interactions	40	58,20
2.	No Drug Interactions antidiabetic	27	41,80
	Total	67	100

Based on Table 2, the results of patients who experienced the incidence of drug interactions were 40 (58.20%) patients who experienced COVID-19 drug interactions with antidiabetics. 27 (41.80%) patients who did not experience covid-19 drug interactions with antidiabetics. Drug interactions can be divided by mechanism of action and severity. Drug interactions based on the mechanism of action are pharmacokinetics and pharmacodynamics while for severity there are categories of moderate (moderate), major (severe), and minor (mild) (Dipiro et al., 2020)

3.3 Distribution of Most Frequent Potential Drug Interactions Between COVID-19 and Antidibetic Drug

Based on table 3, results were obtained for drug interactions that often occur between COVID-19 drugs and antidiabetic drugs, namely the interaction between methylprednisolone and insulin aspart (29.23%). The interaction of methylprednisolone drugs with insulin aspart mechanism interaction is that it can reduce the effectiveness of insulin which can interfere with blood glucose control because it can cause hyperglycemia, glucose intolerance, new-onset diabetes mellitus, and/or exacerbation of pre- existing diabetes (Medscape, 2022). A side effect of insulin is that it can increase the entry of glucose into muscle cells and adipose tissue which can cause levels of glucose to decrease (hypoglycemia). But in the corticosteroid group drugs have side effects, namely, they can increase resistance from insulin, remove glucose from the hepatic and glucose enter the cells inhibited, both muscle cells and adipose tissue which can cause glucose levels in the blood to be high or increase (hyperglycemia) (Medscape, 2022).

Table 3. Distribution of Most Frequent Potential Drug Interaction Between COVID-19 and antidiabetic Drugs

No	Drug Interactions	Severity Levels	Interaction mechanism	Information	Percentage (%)
1.	Methylprednisolone- Insulin Aspart	Moderate	Pharmacodynamics	Lowers the effect of insulin aspart which can interfere with blood glucose control because it can cause hyperglycemia,	29,23
2.	Levofloxacin- aspart	InsulinMayor	Pharmacodynamics	Impaired blood glucose homeostasis that may stem from effects on the potassium canal ATP of pancreatic beta cells that regulate insulin secretion	15,38
3.	Acetylsalicylic acid Insulin glargine	-Moderate	Pharmacodynamics	The hypoglycemia effect of insulin can be amplified by the simultaneous use of Acetylsalicylic acid	3,08

3.4 Distribution of Potential Drug Interactions Base on Severity Levels

Based on Table 3, the majority of potential drug interactions found in COVID-19 patients with type 2 DM were of moderate severity (77,61%), followed by major severity (22.39%). No interactions were found at the minor meaningfulness level. This finding is consistent with Yuniar et al., (2020) research, which noted the high prevalence of drug interactions between COVID-19 medications and comorbidities (Yuniar et al., 2020).

Table 4. Distribution of Potential Drug Interactions Based on Severity Levels in COVID-19 Patients with Comorbid Diabetes Mellitus Type 2 inpatients at Hospitals of South Tangerang City Hospital in 2021

No	Severity Levels	Frequency	Percentage (%)
1.	Major	15	22,39
2.	Moderate	52	77,61
3.	Minor	0	0
	Total	67	100

Potential drug interactions that often occur at moderate levels found are methylprednisolone with insulin aspart. Methylprednisolone is a corticosteroid class drug that has side effects that can increase resistance to insulin and other antidiabetic drugs. If this drug is used simultaneously it will cause a decrease in the effectiveness of insulin aspart then from it will cause side effects of hyperglycemia, glucose intolerance, new-onset diabetes mellitus, and/or exacerbation of pre-existing diabetes (Drugs.com, 2022).

Meanwhile, the potential for major interactions found in this study was in quinolone group antibiotics, namely levofloxacin with insulin aspart, which if the two drugs were used simultaneously caused an interaction of major meaningfulness levels. Because levofloxacin is a quinolone class drug that can interfere with the therapeutic effectiveness of insulin or other antidiabetic drugs. Namely, levofloxacin interferes with blood glucose homeostasis which may stem from effects on the potassium canal ATP of pancreatic beta cells that regulate insulin secretion. Therefore, it causes side effects of hyperglycemia or hypoglycemia for patients who consume levofloxacin with insulin or other antidiabetic drugs (Medscape, 2022).

3.5 Distribution of Potential Drug Interactions Base on the Mechanism of Action

Based on table 5. explained that based on the mechanism of action of the drug, the interaction of COVID- 19 drugs with type 2 DM, the majority of which occurs, is pharmacodynamically (100%). The results of this study are similar to recent studies explaining that the mechanism of action of drug interactions that often occur drug interactions causes synergistic and antagonistic effects (Faizah and Wuryana, 2018). Drug interactions occurring in pharmacodynamic mechanisms can cause fatal effects because if the interaction occurs on a drug, similar drugs also experience drug interactions (Dipiro et al., 2020).

Table 5. Distribution of Potential Drug Interactions Based on the Mechanism of Action of Drugs in COVID-19 Patients with Comorbid Diabetes Mellitus Type 2 in hospitalizations at South Tangerang City Hospital in 2021

No	Mechanism Interactions	Frequency	Percentage (%)
1.	Pharmacokinetics	0	0
2.	Pharmacodynamic	67	100
	Total	67	100

One example is in levofloxacin drugs with insulin aspart which increases hyperglycemic/hypoglycemic effects due to the occurrence of impaired glucose homeostasis in the blood derived from the effect of potassium channels ATP pancreatic beta cells that regulate the secretion system in insulin (Medscape, 2022). As for drug interactions, and pharmacokinetic mechanisms in this study, there was no interaction of COVID-19 drugs with antidiabetics.

3.6 Relationship of drug interaction with clinical outcomes

Based on the analysis of the relationship between the incidence of overall drug interactions and clinical outcomes using the Chi-square analysis which can be seen in table 6. Using the chi-square method and the results obtained there was no meaningful relationship between the variables of drug interaction with clinical outcomes, this can be proven by the result of the value $P = 0.539$ ($p > 0.05$). Research by Anggraini (2015) suggested that there was no proven relationship between drug interactions and blood glucose levels. This conclusion was based on a chi-square test yielding a p-value 0.265. However, research conducted by Ermaralda explained that there is a meaningful relationship between drug interactions and clinical outcomes as evidenced by a value ($p = 0.007$) (Ermaralda, 2016).

Table 6. Relationship of drug interaction with clinical outcomes in COVID-19 patients with Type 2 Diabetes Mellitus in Hospitalizations at South Tangerang City Hospital in 2021.

	GDS < 200 mg/dL		GDS > 200 mg/dL		OR	p-Value
	Frequency	Percentage (%)	Frequency	Percentage (%)		
Drug Interaction	38	56.7	29	43.3	1.31	0.539
No Drug Interaction	15	50.0	15	50.0		
Total	53	54.6	28	45.5		

The difference in the results of this study with previous studies or theories is influenced by several factors, namely the level of meaningfulness and the effects of drug interactions that occur. Pharmacological therapy used by patients, patient adherence to taking medications, other comorbidities, as well as other factors that researchers cannot monitor during conducting studies. Table 5 also shows that the mechanism of drug interactions that occurred was predominantly pharmacodynamic. Pharmacodynamic interactions constitute the majority of clinically important drug interactions. This indicates that the potential for interactions is more likely to occur at the level of the receptor system, physiological system, or the same site of action, resulting in additive, synergistic, or antagonistic effects (Rawitri et al. 2022). Therefore, clinical management must focus heavily on monitoring patient-specific physiological responses and adjusting dosages to mitigate these direct effects.

4. CONCLUSION

Based on the results of research and discussions regarding the identification of drug interactions in COVID-19 Patients with Type 2 Diabetes Mellitus in the Inpatient Hospital of South Tangerang City Hospital for the 2021 Period, it can be concluded as follows: Of the 97 COVID-19 patients with diabetes mellitus, 65 patients experienced drug interactions, and 40 of these interactions occurred between antidiabetic drugs and COVID-19 medications. The most common drug interaction between COVID-19 medications and antidiabetic drugs is methylprednisolone with insulin aspart. Drug interactions occurred at the moderate level (77,61%) in each patient, while for major level interactions (22,39%). the mechanism of interaction occurred pharmacodynamically (100%). There was no significant association between the incidence of drug interactions and clinical outcomes ($P > 0.05$).

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