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RESEARCH ARTICLE

Antidiabetic drug profile of COVID-19 patients with comorbid diabetes mellitus

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Abstract

Background: Diabetes mellitus (DM) is a risk factor that can increase the severity and mortality of patients with COVID-19 infection. The use of antidiabetic drugs for diabetes mellitus patients with COVID-19 infection is very important to reduce these impacts. **Objective:** This study aimed to determine the antidiabetic drug profiles of COVID-19 patients with comorbid diabetes mellitus. **Method:** This study was an analytic cross-sectional electronic medical record data of patients diagnosed with COVID-19 and comorbid Diabetes Mellitus. It was carried out from May until December 2020. **Result:** A total of 106 patients were involved and different types of antidiabetic drugs were used i.e., glimepiride in 32 patients (31.13%), metformin in 18 patients (16.98%), combination of long-acting and rapid-acting insulin in 20 patients (18.87%), and combination of metformin and glimepiride in 18 patients (16.98%). **Conclusion:** The most commonly prescribed single antidiabetic therapy in patients with COVID-19 and comorbid diabetes mellitus was glimepiride, followed by glimepiride and metformin. The most common insulin therapy combination was long-acting and rapid-acting insulin.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The first emergence of this disease was known from a report of a mysterious pneumonia case with an unknown cause on December 31, 2019, in China. The epidemiological data initially showed that 66% of patients were exposed to this virus from an animal and seafood market in Wuhan, Hubei Province, China. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic. A while later, in March 2020, it was first reported in Indonesia (Yuki *et al*., 2020; KEMKES RI, 2020).

Diabetes mellitus (DM) is a risk factor that can increase the severity and mortality of patients with COVID-19 infection. As the immune system dysfunctions in patients with diabetes mellitus, these impacts worsen, especially in the uncontrolled group. Diabetes mellitus patients with COVID-19 infection were more frequently associated with severe or critical conditions because viral infection-induced cell damage, particularly the induction of apoptosis, is exacerbated by hyperglycemia due to elevated reactive oxygen species, and the pro-coagulant state in diabetes promotes the thrombotic effects of severe COVID-19 infection (Singh *et al*., 2020). The Chinese Center for Disease Control and Prevention (China CDC) conducted a case-cohort analysis of 70,000 patients with COVID-19 and reported a mortality rate of 2.3% in non-diabetes mellitus patients and an increase in mortality rate to 7.3% in diabetes mellitus patients (Wu *et al*., 2020). The United States Centers for Disease Prevention and Control (USA CDC) investigated 7,162 patients with COVID-19 and found the prevalence of diabetes mellitus in the outpatient group to be 6%, while non-ICU inpatient

group and ICU inpatient group was 32% (Corrao *et al*., 2021). Previous research on COVID-19 cases in Indonesia showed that diabetes mellitus was ranked the second most common comorbid case with a percentage of 33.6%. COVID-19 Task Force of Indonesia, found in May 2021, the prevalence of diabetes mellitus as a comorbidity among patients with COVID-29 to be 36.6%. (Satuan tugas COVID-19, 2021).

Research related to diabetes mellitus as a comorbid in COVID-19 cases, especially in Indonesia, is rarely done. Diabetes mellitus is one of the most common comorbidities that has a negative influence on the severity and odds of mortality in COVID-19 patients. Patients treated with Metformin for type 2 diabetes during COVID-19 hospitalisation had a lower incidence of intensive care and mortality rates compared to non-metformin patients (Bailey & Gwilt, 2022). In another study, metformin was essentially related to decreased mortality in women with obesity or type 2 diabetes who were admitted to the hospital for COVID-19 (Bramante *et al*., 2021). Therefore, this current study aimed to determine the antidiabetic drug profiles of COVID-19 patients with comorbid diabetes mellitus at the Kogabwilhan II Field Hospital Surabaya. The result of the study could support health management/services for diabetes mellitus patients with COVID-19 infection.

Methods

Design

This study was an analytic cross-sectional study collecting electronic medical record data of patients diagnosed with COVID-19 with comorbid diabetes mellitus. This study was approved by the Ethical Committee from the Faculty of Medicine, Universitas Airlangga, Surabaya based on the registered number of ethical approval No.37/EC/KEPK/FKUA/2021.

Assessment

This study was carried out from May until December 2020 at the Kogabwilhan II Field Hospital Surabaya. Sampling was carried out using the consecutive time-limited sampling technique on patients diagnosed with COVID-19 who met the inclusion criteria for the samples i.e., confirmed-COVID-19, male/female, patients aged ≥18 years old, having diabetes mellitus with or without other comorbidities, and currently receiving diabetes mellitus therapy. Incomplete medical record data were excluded.

Results

The patient's characteristics in this study are shown in Table I.

Table I: Patient's characteristics

Characteristics	Result	
	∑ (n=106)	%
Sex		
Female	58	54.72%
Male	48	45.28%
Age		
26-35 years	9	8.49%
36-45 years	16	15.09%
46-55 years	48	45.28%
56-65 years	29	27.36%
>65 years	4	3.77%
Category of Body Mass Index (BMI)		
Underweight	3	2.83%
Normal	24	22.64%
Overweight	13	12.26%
Obesity I	47	44.34%
Obesity II	19	17.92%
Degree of diabetes mellitus control		
Controlled DM	17	16.04%
Uncontrolled DM	47	44.34%
No data	42	39.62%

Controlled DM: GDP (80-130 mg/dL) and/or GD2JPP (<180 mg/dL)
Uncontrolled DM: GDP >130 mg/dL) and/or GD2JPP (>=180 mg/dL)

A total of 106 patients met the inclusion criteria with a proportion of 58 females (54.72%) and 48 males (45.28%). The majority of the patients were between the ages of 46-55 years (45.28%) and 1 in 47 were obese (44.34%). There were 17 patients (16.04%) with controlled diabetes mellitus, 47 patients (44.34%) with uncontrolled diabetes mellitus, and 42 patients (39.62%) with unknown diabetes mellitus status due to missing GDP data. The observation of the 106 patients showed that diabetes mellitus therapy was given according to the medical history. Diabetes mellitus therapy was generally given as single therapy with oral antidiabetics or insulin or a combination of both drugs, depending on the patient's condition. The antidiabetic drug profile of COVID-19 patients with comorbid diabetes mellitus is shown in Table II.

Table II shows that the most commonly administered single therapy was glimepiride in 33 patients (31.13%), metformin in 18 patients (16.98%), and long-acting insulin in three patients (2.83%). While the most widely administered combination therapy was a combination

of long-acting and rapid-acting insulin in 20 patients (18.87%) and a combination of glimepiride and metformin in 18 patients (16.98%).

Table II: The antidiabetic drug profile of COVID-19 patients with comorbid diabetes mellitus

Drug therapy	∑	%
Single therapy		
Glimepiride	33	31.13
Metformin	18	16.98
Long-acting insulin	3	2.83
Rapid-acting insulin	1	0.94
Combination therapy		
Glimepiride + Metformin	18	16.98
Glimepiride + Insulin detemir	2	1.89
Glimepiride + Insulin glargine	2	1.89
Glimepiride + Insulin glulisine	1	0.94
Glimepiride + Insulin detemir + Insulin glulisine	2	1.89
Glimepiride + Insulin glargine + Insulin lispro	1	0.94
Metformin + Insulin glulisine	1	0.94
Metformin + Insulin glulisine + Insulin detemir	3	2.83
Glimepiride + Metformin + Insulin detemir + Insulin glulisine	20	18.87
Long-acting + Rapid-acting insulin	3	2.83
	20	18.87
Total (n)	**106**	**100**

Discussion

A total of 106 patients met the inclusion criteria for this study. The proportion of female patients was greater in this study. However, recent studies showed that a higher proportion of male patients, because angiotensin-converting enzyme-2 (ACE2) receptor expression was thought to be the main cause of susceptibility to SARS-CoV-2 infection among male patients (Wu *et al*., 2020). Based on the characteristics of body mass index (BMI), 47 patients were obese (44.34%). These findings indicate that obese patients experienced more COVID-19 symptoms compared with overweight and normal weight patients. Jung and the authors also found that overweight and obese patients had a 13% and 25% greater risk of being infected with COVID-19 (Jung *et al*., 2020). Similar results were also obtained in a study conducted on 147 COVID-19 patients at Ramathibodi Hospital Thailand, where 31.3% of the samples were obese (Jayanama *et al*., 2021). From a physiological perspective, several respiratory disorders that can be found in obese patients include: 1) increased intra-abdominal adipose tissue which causes pulmonary compression and a high diaphragm which restricts thoracic respiratory movements and results in decreased residual capacity and tidal volume which causes atelectasis; 2) reduced lung compliance and lung contraction which result in a shortening of both the inner diameter of the airway and the airway smooth muscle, which increases airway resistance; 3) fat accumulation in the soft tissues of the pharynx which increases inspiratory resistance, resulting in decreased airway pressures during inspiration and increased collapsed airway; 4) increased risk of complications of sleep apnea syndrome (Dixon & Peters, 2018; Kimura & Namkoong, 2020). Based on the degree of diabetes mellitus control, 17 patients (16.04%) had controlled DM, 47 patients (44.34%) with uncontrolled DM, and 42 patients (39.62%) with no GDP data. These results might have been influenced by the incomplete medical record. Meanwhile, GDP measurement and documentation should be taken into account in future research to minimise bias. In Hubei Province of China, 7,337 hospitalised confirmed COVID-19 patients with a history of type 2 diabetes mellitus mostly had well-controlled type 2 diabetes mellitus (blood glucose level = 3.9-10 mmol/ L; HbA1c 7.3%) (Zhu *et al*., 2020). However, in this study, the number of patients with uncontrolled DM who developed clinical symptoms was greater than that of patients with controlled DM (50% and 8.49% respectively).

If diabetes mellitus patients with COVID-19 infection have good oral food intake and no nausea/vomiting, metformin can be continued. Metformin as the first line of treatment for diabetes mellitus has previously been known to have antiproliferative and immunomodulating effects. In this study, metformin was most commonly combined with glimepiride. Recent evidence suggests that administering metformin to diabetes mellitus patients with COVID-19 is safe and beneficial. Metformin is thought to have the ability to increase the host immune response by inducing the conversion of adenosine monophosphate (AMP) to AMP-activated protein kinase (AMPK). It also induces autophagy, the formation of M2 macrophages, and CD8 memory T cells. On the other hand, it decreases the expression of genes encoding chemokines and cytokines (Singh & Singh, 2020). It is also considered to have an antioxidant effect on catalase and superoxide dismutase (Diniz Vilela *et al*., 2016). Previous studies also have shown some related results of metformin administration. A well-controlled DM group (39% of patients receiving metformin) showed a more significant reduction in all mortality causes compared to a non-controlled DM group (26% of members receiving metformin) after adjustment (adjusted HR 0.13; 95% CI, 0.04-0.44, p <0.001) (Zhu *et al*., 2020). The metformin-administered group had

significantly higher albumin levels (38.6 vs 36.7 g/L, *p* =0.04) and lower IL-6 levels (4.1 vs 11.1 pg/mL, *p* =0.02) compared to the non-metformin-administered group. Mortality rates during hospitalisation were lower in the metformin-administered group than in the non-metformin-administered group (9.3 vs 19.5%, *p* = 0.19) (Chen *et al*., 2020).

The use of insulin accompanied by constant glucose monitoring is the mainstay of therapy for hospitalised patients with hyperglycemia. An intensive regimen with a combination of basal and prandial insulin is the best therapy for non-critical inpatients with good or poor oral nutritional intake to achieve the recommended blood glucose levels (140-180 mg/dL) (Longo *et al*., 2020). Insulin therapy in diabetes mellitus patients with COVID-19 infection needs to be continued with the adjustment of the insulin dose and other therapies to treat glycemic control status, risk of hypoglycemia, and the severity of the infection. Serum potassium levels always need to be monitored in all COVID-19 patients taking insulin. SARS-CoV-2 can reduce potassium levels and exacerbate insulin-induced hypokalemia through the suppression of ACE2 expression, which causes an increase in angiotensin II levels followed by hyperaldosteronism which will ultimately increase the excretion of potassium through the kidneys (Bornstein *et al*., 2020; Koliaki *et al*., 2020).

In contrast to the direct effects of insulin and metformin, there is no evidence to date showing a relationship between the use of sulfonylureas and the progression of COVID-19 infection (Chee *et al*., 2020; Koliaki *et al*., 2020). The factor that impacts the broad utilisation of glimepiride in COVID-19 patients with comorbid diabetes mellitus at Kogabwilhan II Field Hospital Surabaya is the patient's medical history.

Conclusion

The widely used single oral antidiabetic therapy in COVID-19 patients with comorbid diabetes mellitus was glimepiride and the most given combination oral therapy was glimepiride and metformin. Long-acting and rapid-acting insulin was the most combination of insulin therapy.

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