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Cost Consequence Analysis of Antidiabetic Therapy in Covid-19 Hospitalized Patients with Diabetes Mellitus at Panembahan Senopati Hospital Yogyakarta

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ABSTRACT

One of the significant respiratory infections is Covid-19, and its occurrence in Indonesia varies due to the diverse geographical positions across the region. Therefore, demographic groups consisting of individuals of a certain age and those with certain medical conditions remain at the highest risk of contracting Covid-19. The severity of Covid-19 patients are greatly influenced by underlying health conditions such as diabetes mellitus, hypertension, age, and obesity. In particular, diabetes mellitus is associated with an increased risk of severe illness and mortality among Covid-19 patients, potentially impacting healthcare expenditure, especially pharmaceutical costs. Therefore, this study aims to describe the financing of medication therapy, the outcomes of antidiabetic therapy, and the average direct medication costs inpatients with Covid-19 at Panembahan Senopati Hospital. Using a non-experimental descriptive-analytic approach, this study retrospectively collected data from medical records from 2020 to 2021. The results showed: 1) a description of diabetes mellitus treatment therapy with Covid- 19, namely the most common single therapy is the use of insulin, namely Novorapid and Novomix, a combination therapy of 2 drugs, namely Metformin + Novorapid, while a combination therapy of 3 drugs, namely Metformin + Novorapid + Glibenclamide 2) the achievement of therapeutic outcomes in diabetic patients with Covid-19 who received therapy as many as 77.27% of patients reached the target and 22.73% of patients had not reached the target glucose level 3) the average direct treatment cost of hospitalized diabetes mellitus patients with Covid-19 was IDR. 5,234,858 per patient based on the hospital's perspective.

INTRODUCTION

Diabetes mellitus referred to as a chronic degenerative condition, Diabetes mellitus carries an increased risk of complications and accompanying health problems. It is one of the challenges and has a huge impact both epidemiologically and economically. (Lorenzoni et al., 2017). Southeast Asia holds the third position globally in terms of the prevalence of diabetes mellitus, standing at 11.3%, as per projections by the International Diabetes Federation (IDF, 2021), Among the countries in the Southeast Asian region, Indonesia is among ranking seventh with a population of 10.7 million. This underlines Indonesia's important role in the number of diabetes cases in Southeast Asia (Cahyaningrum, 2023).

About 4.8% of the Indonesian populace is afflicted by diabetes mellitus, with over half of these cases (58.8%) remaining undiagnosed. It is estimated that by 2030, around 21,3 million Indonesians will suffer from diabetes (Nasution et al., 2021). Yogyakarta Special Region Province has the 3rd highest. Prevalence of DM in Indonesia with the largest age group being 55-64 years old. Diabetes mellitus is the second disease in the top 10 most common diseases in 2021(Kemenkes, 2019; Dinkes DIY, 2022).

Diabetes is one of the main risk factors that cause COVID-19 to become more severe. In addition, the disease is also a global health threat whose severity has been increasing in the past two decades. Diabetes causes the general health condition of Covid-19 patients to worsen. The disruption of the innate immune system, which is the body's initial defense against SARS-CoV- 2, is one of the mechanisms underlying the increased risk of Covid-19 in patients with type 2 diabetes mellitus (Panua et al., 2021). The disruption of the activation of this adaptive immune response will inhibit immune stimuli delivered by Th1 cells, resulting in a delayed hyperinflammatory reaction. Reduced T cell function will result in dysfunction in the innate immune system and cause a cytokine storm resulting in extensive inflammation of the lungs, Acute Respiratory Distress Syndrome (ARDS), and multi-organ dysfunction, including an increased risk of being infected with Covid-19 (Panua et al., 2021). Immune system disorders in type 2 diabetes mellitus are associated with abnormal production of proinflammatory cytokines, especially TNF α and IFN, which are also detected in patients affected by Covid-19 (Panua et al., 2021).

Treatment of diabetes mellitus requires long-term therapy. The use of antidiabetic drugs consists of the selection of single or combination drugs. The goal of antidiabetic treatment in patients affected by Covid-19 is to achieve therapeutic outcomes, namely the patient's current blood glucose <200 mg/dL (Perkeni, 2021). Treatment therapy for patients with diabetes mellitus is a concern when patients experience Covid-19. Interventions are needed for Covid-19 patients with diabetes to achieve a better quality of life for patients. Based on this background to determine the description of antidiabetic drug therapy in patients, determine the outcome of antidiabetic therapy in patients, and determine the direct medical costs.

From an economic perspective, the diabetes epidemic imposes financial costs as the prevalence and complications associated with the condition increase. This trend is expected to drive the development of health technology assessment (HTA), especially with the issue of diseases caused by Covid-19 (Fatimah et al., 2022).

METHODS

Research Design

This study used a non-experimental approach designed descriptively using medical records as cross-sectional secondary data. This study explores health phenomena that occur from medical record data descriptively. The calculation of costs is seen from the hospital's point of view, namely direct costs including antidiabetic costs, other drug costs, service costs, hospitalization costs, medical devices, diagnostic costs, and service costs. This research has received research approval from the Ahmad Dahlan University research ethics committee with the administrative number 022307099.

Population and Sample

The population in this sample is a single diabetes mellitus patient diagnosed with COVID-19 who was treated at Panembahan Senopati Hospital Yogyakarta in 2020-2021. The number of samples was not determined in this study.

Data Collection Technique

Sampling was conducted the usage of puIDRosive sampling technique primarily based on criteria. The inclusion criteria were inpatients, age ≥ 18 years, single primary diagnosis of diabetes mellitus with Covid- 19, patients with medical record, and complete cost information. Medical record data included patient identity (gender, age, and medical record number), current blood glucose data, swab or PCR test results, diagnosis, length of hospitalization, and details of drugs given. Cost details included hospitalization costs, maintenance costs, and supporting costs. Exclusion criteria included deceased patients and incomplete medical record data.

Data analysis to measure costs based on the hospital's perspective is as follows:

1. Data on patient characteristics include gender, age, and length of hospitalization.
2. The description of diabetes mellitus treatment therapy includes drug class, drug name, drug dosage strength.
3. The calculation of therapeutic outcomes become decided based on the proportion of patients who achieved the goal blood sugar control (GDS) divided by means of the range

of patients who received certain types of antidiabetic therapy.
4. The calculation of direct medical cost components includes antidiabetic drug costs, other drug costs, service costs, laboratory costs, medical device costs, and other supporting costs.

RESULTS AND DISCUSSION

Patient Characteristics

The findings from the research conducted at Panembahan Senopati Hospital Yogyakarta indicated that 22 Covid-19 patients with diabetes mellitus met the inclusion criteria. Data collection spanned from April 2020 to December 2021. Among these patients, 22 were categorized based on age, gender, and duration of hospital stay. As per the data presented in

Table 1. Characteristics of Covid-19 Diabetes Mellitus Patients at Panembahan Senopati Hospital

Patient Characteristic	Group	Jumlah pasien	Persentase (%)
Gender	Men	9	40.91
	Woman	13	59.09
	Total	22	100
Age	(36-45)	4	18.18
	(46-55)	7	31.82
	(56-65)	7	31.82
	> 65	4	18.18
	Total	22	100
LOT	<7 Days	3	13.64
	7-14 Days	17	77.27
	15-25 Days	2	9.09
	Total	22	100

Table 1, a significant proportion of diabetes mellitus cases occurred in women, accounting for 22 patients, constituting 59.09% of the total. The prevalence of diabetes mellitus in women suIDRassed that in men. Regarding risk factors, women are predisposed to diabetes mellitus, potentially due to factors such as a higher likelihood of increased body mass index and hormonal changes post-menopause, leading to rapid accumulation of body fat (Fransiska, 2016). Fat that accumulates in the body will cause insulin resistance because excess fat causes free fatty acids in the cell to increase. Therefore, diminishing the movement of glucose transporters to the cell's outer membrane (Teixeira-Lemos et al., 2011). The buildup of fat can heighten the risk of obesity, which, in turn, becomes a contributing factor to diabetes mellitus. This occurs due to the hindrance of glucose absorption into muscle and fat cells, consequently leading to elevated blood glucose levels (Yosmar et al., 2011). The effect of obesity on DM can be caused by unhealthy behavior (Prasetyani, 2017).

According to the information provided in **Table 1**, diabetes mellitus predominantly occurs within the age bracket of 46-55 years, with 15 patients accounting for 37.5% of the total. These results are the opinion of Perkeni 2021, which states that those over 45 years of age are a group at risk of suffering from diabetes mellitus (Perkeni, 2021). Furthermore, this aligns with the International Diabetes Federation (IDF) data from 2013, indicating that individuals with prediabetes fall within the age group of 40-59 years. Approximately 80% of individuals with diabetes are situated within the 40-59 age range in developing nations like Indonesia. (IDF, 2014).

Relationship between age and the prevalence of increased blood glucose levels. this is because of the aging method in order to cause modifications inside the anatomy, body structure, and biochemistry of the body (Prasetyani, 2017). In addition, at an older age, they will experience a decrease in mitochondrial activity in muscle cells by 35%, and the fat content in muscle will increase by 30%. One of the impacts is increased insulin resistance (Madelina et al., 2018).

Increased insulin has an impact on the condition of the body; it becomes resistant to insulin, so there is no stability of blood sugar, which causes the risk of one of DM due to age. Ageing outcomes in changes in carbohydrate metabolism, changes in insulin release that's influenced via blood glucose, and inhibition of blood glucose release. At an older age, they also have a sedentary lifestyle or do not have a balanced pattern (Prasetyani, 2017).

Overview of Antidiabetic Therapy

Patients included in the study subjects were diabetes mellitus patients who were hospitalized using combination therapy of oral antidiabetics with oral, oral antidiabetics with insulin, and

insulin with insulin. Antidiabetic combination therapy is given when single antidiabetic therapy cannot achieve the therapeutic target. When used separately or as a fixed-dose combination, oral combination antidiabetic drugs require the use of 2 types of drugs with different mechanisms of action. The choice of medication for each individual is tailored to the patient's current condition and severity. The success of therapy depends on the selection of the right drug. Determination of drug regimens must consider the severity and health conditions of the patient, including comorbidities and other complications (Fransiska, 2016).

The drugs to be given to patients must refer to the national formulary. The 2023 national formulary lists oral antidiabetics, parenteral antidiabetics, and insulin analogs. The formulary lists oral antidiabetic drugs consisting of acarbose, glibenclamide, gliclazide, glikuidone, glimepiride, glipizide, metformin, pioglitazone and parenteral antidiabetics consisting of human insulin (rapid-acting insulin, intermediate-acting insulin, long-acting insulin) and insulin analogs (rapid-acting insulin). Fast-acting insulin, intermediate-acting insulin, long-acting insulin). This study found that the oral antidiabetic drugs were glibenclamid, glimepiride, and metformin. While the parenteral antidiabetic drugs used fast-acting and long-acting insulin.

Data in **Table 2** shows that the most widely used single therapy is insulin, namely Novomix and Novorapid. While the most widelyused combination was the combination of biguanide (Metformin 500 mg tablets) with insulin aspart (Novorapid) which is a fast-acting insulin with a percentage of 18.18%. This drug combination can reduce blood glucose levels to stable values. Blood glucose levels remain controlled even though the duration of insulin administration has expired because the effect of metformin has a longer duration. Research Hemmingsen et al. (2012) proved that the combination of insulin and metformin can reduce HbA1c levels by 0.5% and minimize weight gain, side effects of insulin (Baroroh et al., 2016).

Table 2. Description of Antidiabetic Therapy Hospitalized at Panembahan Senopati For The 2020-2021 Periode

Group Therapy	Therapy Class	Drug name and dosage strength	Number of patients	Percentage (%)
Single orally	Biguanide	Metformin tab 500 mg	2	9.09
	Sulfonylureas	Glimepiride tab 2 mg	1	4.55
Single Insulin	Mixed insulin analogs	Novomix (combination of 70% insulin protamine aspart and 30%insulin aspart)	3	13.64
	Prandial Insulin Analogues	Novorapid (Insulin aspart)	3	13.64
Combinationof 2 antidiabetics Oral - Insulin	Biguanide + Mixed insulin analogue	Metformin tab 500 mg + Novomix (combination of 70% insulin protamine aspart and 30% insulinaspart)	2	9.09
	Biguanide + Prandial Insulin Analogue	Metformin tab 500 mg + Novorapid (Insulin aspart)	4	18.18
	Sulfonylureas + Prandial InsulinAnalogs	Glimepiride tab 2 mg + Novorapid(Insulin aspart)	1	4.55
Combinationof 2 antidiabetics Insulin -Insulin	Prandial Insulin Analogue + insulin detemir (Long term insulin)	Novorapid (Insulin aspart) + Levemir	1	4.55
	Mixed insulin analogue + PrandialInsulin Analogue	Novomix + Novorapid (Insulin aspart)	1	4.55
Combinationof 3 oral antidiabetics - insulin -oral	Biguanide + Prandial Insulin Analogue + Sulfonylureas	Metformin tab 500 mg + Novorapid(Insulin aspart) + Glimepiride tab 2 mg	1	4.55
	Biguanide + Prandial Insulin Analogue + Sulfonylureas	Metformin tab 500 mg + Novorapid(Insulin aspart) + Glibenclamide tab 2.5 mg	2	9.09
Combinationof 3 oral antidiabetics - insulin -insulin	Biguanide + Prandial Insulin Analogue + Mixed insulin analogue	Metformin tab 500 mg + Novorapid(Insulin aspart) + Novomix	1	4.55

Outcome of Antidiabetic Treatment

Treatment effectiveness was measured by examining the percentage of patients who achieved insulin receptor sensitisation and blood glucose targets during single or combination antidiabetic therapy, relative to the

total number of patients receiving the same treatment regimen. This study uses blood glucose levels (GDS) as a parameter of successful therapy in achieving glucose targets in patients. The goal of oral antidiabetic therapy in patients is to maintain blood sugar levels within routine parameters (≤ 200 mg/dL) (Perkeni, 2021).

The comparison of blood glucose levels before and after inpatient treatment is illustrated in **Table 3** which shows the difference in instantaneous blood glucose levels. The outcome of antidiabetic therapy was assessed by dividing the percentage of patients who achieved their blood sugar target by the total number of patients in the respective treatment group.

Table 3. Reduction in Blood Glucose Levels During Hospital Stay

Indicator	Baseline blood sugar(mg/dL)	Blood sugar afterward (mg/dL)
Average	310.73	192.55
SD	73.58	76.08

Based on the findings in this study, out of a total of 22 patients, 17 of them recovered successfully, while 5 patients did not recover. Research by Fahmia et al., (2022) showed that patients with risk factors of severe severity, anosmia, diabetes mellitus, fever, male gender, and pneumonia features had a significant association with the duration of hospitalization and recovery rate in patients confirmed with Covid-19.

The description of therapy achievement in diabetes mellitus patients treated at Panembahan Senopati Hospital is presented in **Table 4**. The data shows the results of therapy based on blood sugar in patients with DM 6 therapy regimens have therapeutic results up to 100%.

Although the results of therapy in the group obtained results with perfect scores cannot be concluded as the best therapeutic results compared to other group therapies because the number of research subjects from all groups is only 1-2 people. Based on data calculations, the Novorapid insulin group showed the highest percentage of all therapy groups with 3 patients. This research conducted by Cahyaningsih (2019) proves that disposable insulin, namely Novorapid, has the highest percent reduction rate of blood glucose/day of 13.94% while Novomix type insulin has the lowest percent reduction rate of blood glucose/day of 0.22%. Oral therapy regimens showed good therapeutic results of 100% in each metformin and glimepiride group.

Patients with insulin combination therapy, Novorapid+Levemir and Novomix+Novorapid, based on medical record data, did not show significant blood sugar reduction over time. This is thought to be because the rate of glucose reduction is so slow that it does not meet therapeutic targets. Diabetes mellitus (DM) has the potential to increase the severity and mortality of COVID-19, as well as increase the risk of respiratory failure, cardiac complications, and the need for intensive care in the intensive care unit (ICU).

The cause is believed to be mild chronic inflammation, impaired immune response, and abnormal blood clotting in patients with DM (Balqis et al., 2021). The patient's elevated blood glucose levels stemmed from the COVID-19 infection directly, due to the inflammatory response and increased levels of interleukin (IL)-6 and tumour necrosis factor (TNF)-α during the cytokine storm phase. This causes insulin resistance in peripheral tissues and impairs insulin secretion (Anggiswari, 2022).

Diabetic individuals who contract COVID-19 should maintain adherence to their prescribed treatment plan. According to Balqis et al. (2021) Using medications like metformin, sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors as a preventive measure is not advisable for patients with type 2 diabetes mellitus experiencing severe Covid-19 infection. Additionally, pioglitazone is not suitable for diabetic patients with Covid-19, as it could exacerbate heart failure. In contrast, GLP-1 receptor agonists (GLP-1RAs) and insulin have the capacity to reduce blood glucose levels and reduce inflammation associated with COVID-19. For critically ill patients with type 2 diabetes mellitus infected with Covid-19, the role of insulin is given to patients as an intensive therapeutic approach (Al-kuraishy et al., 2021).

Direct Medical Cost Component

The cost evaluation in this research was carried out from the hospital's perspective. Direct medical expenses considered in this study encompass the expenditure on antidiabetic medications, non-antidiabetic drugs, service charges, laboratory fees, additional support expenses, and medical equipment costs.

Based on **Table 4**, the highest direct medical costs are in the medical equipment cost component, which is an average of IDR. 292,260. This is related to the treatment of people with Diabetes Mellitus who are at great risk of contracting COVID-19 and causing the patient's health condition to worsen. Diabetes mellitus will increase the severity or critical condition of the sufferer. COVID-19 cases with severe risks require special incentive care, resulting in higher medical equipment costs. Table 5 shows that the lowest cost of therapy is in a single oral regimen, namely glimepiride therapy, which averages a total cost of IDR. 1,502,376 during the inpatient treatment period. The lowest cost component is in the cost of the antidiabetic drug component which is IDR. 1,870 with the highest cost component in Nursing costs and procedures which amounted to IDR. 2,592,000. he highest direct medical costs were found in the insulin-insulin therapy group, namely the Novorapid + Levemir therapy group with an average cost of IDR. 14,156,750. The highest direct medical cost component in Novorapid + Levemir therapy is the medical device cost component, which is IDR. 12,722,309.

This is related to the severity or Covid-19 status of diabetic patients which will affect the costs that must be incurred by patients. The more severe the patient's condition, the higher the medical costs incurred, because therapy not only aims to manage diabetes mellitus but also to overcome the risks or complications arising from Covid-19 experienced by the patient.

Table 4. Results of antidiabetic therapy in Covid patients with diabetes mellitu

Group Therapy	Therapy Class	Number of patients	Number of patients who reached the target	The number of patients who did not reach the target	*Yield* (%)	Not achieved (%)
Single orally	Biguanide	2	2	0	100	0
	Sulfonylureas	1	1	0	100	0
Single Insulin	Mixed insulin analogs	3	2	1	66.67	33.33
	Prandial Insulin Analogues	3	3	3	100	0
Combination of 2 antidiabetics Oral – Insulin	Biguanide + Mixed insulin analogue	2	1	1	50	50
	Biguanide + Prandial Insulin Analogue	4	3	1	75	25
	Sulfonylureas + Prandial Insulin Analogs	1	1	0	100	0
Combination of 2 antidiabetic Insulin - Insulin	Prandial Insulin Analogue + insulin detemir (Long term insulin)	1	0	1	0	100
	Mixed insulin analogue + Prandial Insulin Analogue	1	0	1	0	100
Combination of 3 oral antidiabetics – insulin - oral	Biguanide + Prandial Insulin Analogue + Sulfonylureas	1	1	0	100	0
	Biguanide + Prandial Insulin Analogue + Sulfonylureas	2	2	0	100	0
Combination of 3 oral antidiabetics – insulin – insulin	Biguanide + Prandial Insulin Analogue + Mixed insulin analogue	1	1	0	100	0

Table 5. Direct medical cost Components for Covid-19 Diabetes Mellitus Inpatients at Panembahan Senopati Hospital

Group Therapy	Group	Number of patients	Direct Medical Costs(mean ± SD (%)) x 1000							
			Nursing costs and procedures	Doctor service fee	Laboratory fee	Medical eqipment cost	Cost of antidiabetic drugs	Other medical expenses	Hospitalization fee	Average class cost
Single orally	Biguanide	2	2,819 ± 917	924 ± 10	3,026 ±169	2,748 ± 188	207 ±103	3,829 ±302	2,077 ±157	3,336
	Sulfonylureas	1	2,592 ±0	390±0	691 ±0	74±0	1,870 ± 0	1,009± 0	1,250±0	1,502
Single Insulin	Mixed insulin analogs	3	2,794 ± 96	1,008± 149	3,168 ± 411	5,539± 2,652	113 ± 0	6,615± 1,878	2,740 ± 141	5,448
	Prandial Insulin Analogues	3	2,362 ± 330	1,106 ±209	3,486 ± 1,112	4,794 ± 1,874	95 ± 0	6,498± 600	2,400 ± 195	4,852
Combination of 2 antidiabetics Oral – Insulin	Biguanide + Mixed insulin analogue	2	2,548 ± 121	751 ± 9	2,806 ± 329	8,216± 2,184	117 ± 0	5,902± 1,539	2,880±0	4,878
	Biguanide + Prandial Insulin Analogue	4	3,042 ± 1,175	927 ± 306,687	3,495 ± 1,462	8,517± 3,843	98 ±1,188	4,753± 2,022	3,187 ± 897	6,191
	Sulfonylureas + Prandial Insulin Analogs	1	1,433 ±0	371 ±0	1,691±0	2,307± 0	100± 0	2,021±0	1,440±0	2,341
Combination of 2 antidiabetic Insulin - Insulin	Prandial Insulin Analogue + insulin detemir (Long term insulin)	1	7,276 ±0	4,688 ± 0	9,968±0	12,722±0	185± 0	3,570±0	6,480±0	14,156
	Mixed insulin analogue + Prandial Insulin Analogue	1	2,887 ±0	1,023 ±0	3,949± 0	3,481±0	208± 0	5,364±0	3,390±0	5,076
Combination of 3 oral antidiabetics – insulin - oral	Biguanide + Prandial Insulin Analogue + Sulfonylureas	1	1,695 ±0	1,052 ±0	3,040± 0	2,668± 0	103± 0	3,570±0	2,880±0	3,752
	Biguanide + Prandial Insulin Analogue + Sulfonylureas	2	4,329 ± 2,562	352 ±151	2,230 ± 1,404	3,428± 3,288	99±	1,133± 943	1,455 ±705	3,338
Combination of 3 oral antidiabetics – insulin – insulin	Biguanide + Prandial Insulin Analogue + Mixed insulin analogue	1	1,597 ±0	866 ± 0	4,037± 0	12,335 ±0	212± 0	3,678±0	2,400± 0	6,281
Average cost of medical cost components			1,448	615	1,923	2,929	70	2,685	1,529	
Average Direct Medical Costs of Covid-19 Inpatients with Diabetes Mellitus										5,096 ± 3,074

CONCLUSIONS

The general description of diabetes mellitus treatment therapy with COVID-19 is that the most common single therapy is the use of insulin, namely Novorapid and Novomix, a combination therapy of 2 drugs, namely Metformin + Novorapid, while a combination therapy of 3 drugs is Metformin + Novorapid + Glibenclamide. The achievement of therapeutic outcomes in patients with Covid-19 diabetes mellitus who received therapy was 77.27% of patients reached the target, 22.73% of patients had not reached the target glucose level and the average direct treatment cost of hospitalized diabetes mellitus patients with Covid-19 was

IDR 5,234,858 per patient based on the hospital perspective. It is hoped that this research can become a reference for hospitals in choosing anti-diabetic therapy to reduce health costs, especially therapy for Covid-19 patients with diabetes mellitus.

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AUTHORS' CONTRIBUTIONS

All authors contributed equally to conducting this research.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this article.

ETHICAL CONSIDERATION

This research has been approved by the Health Research Ethics Committee of Ahmad Dahlan University research ethics committee with the administrative number 022307099.

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