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Cost-Effectiveness Analysis of Triple Oral Antidiabetic Drug Combination in Patients with Type 2 Diabetes Mellitus: An Outpatient Study in Indonesia

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Abstract

Background. Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. Initial therapy for type 2 diabetes typically starts with metformin monotherapy, but because of its progressive nature, combination therapy is often required to achieve glycemic targets. However, research on combination therapy with three oral antidiabetic drugs is currently limited.

Objective. This study assessed direct medical costs and the cost-effectiveness of a combination of triple oral antidiabetics with first-line metformin combined with glimepiride, pioglitazone, and DPP-4 inhibitors (sitagliptin / vildagliptin), among type 2 DM patients treated in the outpatient clinic of dr. Ramelan Central Naval Hospital, Surabaya, Indonesia.

Methodology. A retrospective cross-sectional analysis was conducted from the hospital perspective using medical records and cost data from January to December 2024. Eligible patients had type 2 DM, received a combination of triple oral antidiabetics with metformin as first-line treatment combined with glimepiride, pioglitazone, and DPP-4 inhibitors (sitagliptin / vildagliptin), attended monthly follow-ups, had at least two HbA1c measurements, and had complete clinical and cost data. Direct medical costs included doctor services, drug acquisition costs, and laboratory monitoring costs.

Results. A total of 79 patients were included, 60.8% male, with an average (SD) age of 54.9 (9.26) years, and 69.6% with comorbidities. Compared with the combination of metformin + glimepiride + pioglitazone, the combination of metformin + sitagliptin / vildagliptin + glimepiride and metformin + sitagliptin / vildagliptin + pioglitazone was more cost-effective, with ICER values of IDR -162,119.77; IDR 845,655.5, respectively. Both ICER values were below the willingness-to-pay (WTP) threshold. One-way sensitivity analysis showed that the model results were relatively robust to parameter variations of ±20%. In the combination of metformin + sitagliptin / vildagliptin + glimepiride vs metformin + glimepiride + pioglitazone, laboratory monitoring costs had the greatest influence on the ICER value. Meanwhile, the combination comparison metformin + sitagliptin / vildagliptin + pioglitazone vs metformin + glimepiride + pioglitazone was most sensitive to changes in effectiveness (ΔHbA1c).

Conclusion. Metformin + sitagliptin / vildagliptin + glimepiride and metformin + sitagliptin / vildagliptin + pioglitazone are both more cost-effective compared to metformin + glimepiride + pioglitazone in this setting.

Key words: type 2 diabetes mellitus, metformin, dipeptidyl-peptidase IV inhibitors, cost-effectiveness analysis, drug combinations; Indonesia

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia and impaired metabolism of carbohydrates, fats, and proteins. Hyperglycemia can lead to several macro and microvascular complications.[1] High blood glucose can lead to complications in various organs such as the eyes, kidneys, nerves, and heart. Type 2 DM is a multifactorial condition characterized by increased chronic disability and a high risk of cardiovascular disease (CVD) and obesity, thus increasing patient morbidity and mortality.[2]

Data from the International Diabetes Federation (IDF) indicates that 589 million adults (20-79 years old) are living with diabetes worldwide. By 2024, Indonesia ranked fifth globally in diabetes prevalence, with the number of patients reaching 20.43 million. The total cost of DM treatment

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globally is estimated to reach USD 1.015 trillion in 2024, with USD 246 billion in the Western Pacific region.[3] According to the American Diabetes Association (ADA), by 2022, the annual cost of diabetes in the US will reach USD 413 billion, including USD 307 billion for direct healthcare costs and USD 106 billion related to decreased productivity.[4] A study in Surabaya (Indonesia) reported that the total cost of DM with complications reached more than IDR 2.6 billion, with an average of IDR 15.7 million per patient.[5]

Initial therapy for type 2 diabetes generally begins with metformin monotherapy, but due to its progressive nature, a combination of drugs is often required to achieve glycemic targets.[4] Based on the Indonesian Endocrinology Association (PERKENI) guidelines, if the HbA1c target is not achieved within 3 months, a combination of two to three drugs with different mechanisms can be given. Commonly used combinations include metformin with a sulfonylurea (glimepiride), a thiazolidinedione (pioglitazone), or a DPP-4 inhibitor (vildagliptin or sitagliptin).[6] The use of three antidiabetic drugs has also been shown to be effective in achieving glycemic control with a lower risk of hypoglycemia, such as the combination of metformin, DPP-4i, and glimepiride or pioglitazone.[1,2]

Given the substantial economic burden of T2DM and the limited evidence regarding triple oral antidiabetic therapy in Indonesia,[7] treatment decisions should consider both clinical outcomes and economic consequences to ensure rational use of healthcare resources.[8] However, research on combination therapy with three oral antidiabetic drugs is currently limited.[7] This study aims to analyze the direct medical costs and cost-effectiveness of using triple oral combination antidiabetics, including glimepiride (SU), pioglitazone (TZD), and vildagliptin or sitagliptin (DPP-4i) with metformin as first-line therapy in outpatients with type 2 diabetes at dr. Ramelan Central Naval Hospital, Surabaya, Indonesia. Dr. Ramelan Central Naval Hospital is a Type A tertiary advanced healthcare facility (FKTL) in Indonesia that provides advanced subspecialty care for patients with complex medical conditions.

METHODOLOGY

Subjects, materials, and methods

This study has received ethical approval from the Research Ethics Committee of the dr. Ramelan Central Naval Hospital, Surabaya, Indonesia, under number 25 / EC / KEP / 2025. This study was conducted from the healthcare provider perspective.

Study subjects

The study subjects included T2DM patients who received combination therapy with triple oral antidiabetic drugs (metformin + sitagliptin / vildagliptin + glimepiride), (metformin + sitagliptin / vildagliptin + pioglitazone), and (metformin + glimepiride + pioglitazone) in the outpatient department of dr. Ramelan Central Naval Hospital, Surabaya, Indonesia, from January 2024 to December 2024. Subject selection was carried out using the total sampling method, which included all patients who met the inclusion criteria: patients with a primary diagnosis of type 2 DM; using a combination of triple oral antidiabetic drugs with first-line metformin and combined with glimepiride, pioglitazone, and / or vildagliptin / sitagliptin; undergoing combination therapy for the first time in the period January-December 2024; routinely conducting monthly check-ups at two HbA1c measurement points within one year; and having complete medical record data and cost details. Patients who died or had specific conditions that could affect HbA1c levels, such as anemia or hypothyroidism, were excluded from the study.

Data collection procedure

Data were collected retrospectively from patient medical records, and details of direct medical costs were obtained from the hospital's Hospital Management Information System (SIMRS). Data were extracted without direct patient identifiers. During the extraction process, data was anonymized by replacing patient identifiers with codes. The data collected included patient characteristics (age, sex, diagnosis, comorbidities, and HbA1c values), as well as direct medical cost components, including doctor services, drug acquisition, and laboratory monitoring.

Data processing and analysis

The data obtained were analyzed using descriptive and inferential approaches. Descriptive analysis was used to describe patient characteristics, details of direct medical costs, and the effectiveness of therapy based on the average reduction in HbA1c levels at two test points. Mean HbA1C reduction(ΔHbA1c)was calculated as the difference between baseline HbA1c (before the patient started triple therapy with oral antidiabetic drugs) and final HbA1c (3-9 months after the patient started triple therapy with oral antidiabetic drugs) for each patient.

A cost-effectiveness analysis was performed by calculating the Average Cost-Effectiveness Ratio (ACER) and the Incremental Cost-Effectiveness Ratio (ICER) for each combination of antidiabetic therapies. Inferential analysis was performed by conducting a comparative test of categories and direct medical costs. To confirm the cost-effectiveness of the combination of triple oral antidiabetics, the ICER value was compared with a willingness to pay threshold of 1–3 times Indonesia's gross domestic product (GDP) per capita (GDP per capita in 2022 = Int$14,445.7), in accordance with the WHO-CHOICE guidelines and the Health Technology Assessment guidelines in Indonesia.[9] Therefore, the willingness to pay threshold in this study was Int$14,445.7 per unit of effectiveness.

Additionally, a one-way sensitivity analysis was conducted by varying the cost of doctor services, drug acquisition,

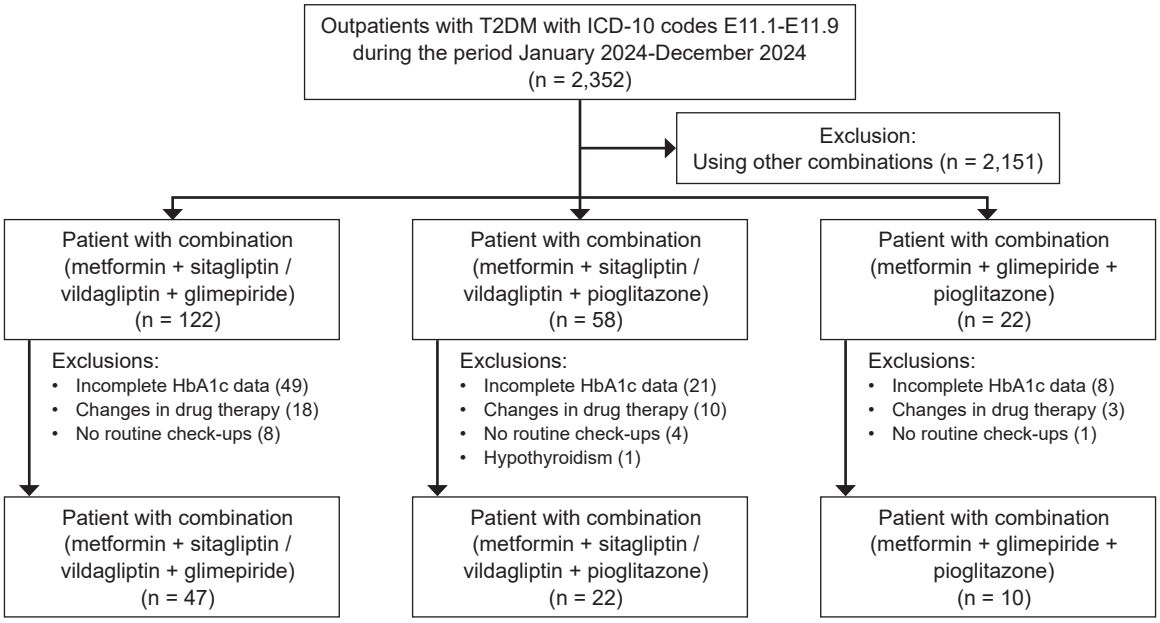

Figure 1. Study flowchart.

Table 1. Patient characteristics

Characteristics	a (n = 47)	b (n = 22)	c (n = 10)	Total (n = 79)	*p*
Sex					
Male	27 (57%)	15 (68%)	6 (60%)	48 (60.8%)	0.70†
Female	20 (43%)	7 (32%)	4 (40%)	31 (39.2%)	
Average age (years)	55.68 ± 8.32	53.41 ± 11.84	54.8 ± 7.28	54.9 ± 9.26	0.64‡
Diagnosis (ICD-10)					
E11.2 (T2DM with renal complications)	5 (9.6%)	3 (11.1%)	1 (7.7%)	9 (9.8%)	0.47†
E11.4 (T2DM with neurological complications)	4 (7.7%)	4 (14.8%)	1 (7.7%)	9 (9.8%)	
E11.5 (T2DM with peripheral circulatory complications)	12 (23.1%)	7 (25.9%)	2 (15.4%)	21 (22.8%)	
E11.7 (T2DM with multiple complications)	17 (32.7%)	5 (18.6%)	5 (38.5%)	27 (29.3%)	
E11.8 (T2DM with unspecified complications)	14 (26.9%)	7 (25.9%)	4 (30.7%)	25 (27.2%)	
E11.9 (T2DM without complications)	0	1 (3.7%)	0	1 (1.1%)	
Comorbidities					
No	14 (29.8%)	6 (27.3%)	4 (40%)	24 (30.4%)	0.76†
Yes	33 (70.2%)	16 (72.7%)	6 (60%)	55 (69.6%)	

a = (metformin + vildagliptin / sitagliptin + glimepiride), b = (metformin + vildagliptin / sitagliptin + pioglitazone), c = (metformin + glimepiride + pioglitazone), p >0.05 not significant; † Chi-Square, ‡ One-way anova

laboratory monitoring, and ΔHbA1c by ±20%, resulting in a change in the ICER value. The results of the analysis are presented in the form of a tornado diagram to show the variables with the most significant impact on the analysis results.

RESULTS

Study population

A total of 2,352 outpatients were diagnosed with type 2 diabetes mellitus at the dr. Ramelan Central Naval Hospital from January 2024 to December 2024. Seventy-nine patients met the inclusion criteria. The study flowchart is shown in Figure 1.

The majority of patients in this study were male (60.8%), with an average age of 54.9 years. The most common diagnosis was E11.7 (Type 2 DM with multiple complications), accounting for 29.3% of patients. Most patients had at least one comorbidity (69.6%), such as hyperlipidemia, hypertension, stroke, hyperuricemia, musculoskeletal, and heart disease. Inferential analysis showed no significant differences between characteristics and antidiabetic combinations (p >0.05) (Table 1).

Direct medical cost

Patients using the antidiabetic combination (metformin + sitagliptin / vildagliptin + pioglitazone) had the highest total direct medical costs compared to other combinations (Table 2). The average cost of doctor services for each antidiabetic combination was the same, at IDR 150,000.

Based on inferential analysis using the non-parametric Kruskal-Wallis test, a significant difference was found between the average total direct medical costs (p <0.05) and the drug acquisition costs of antidiabetic drugs (p <0.05)

Table 2. Direct medical cost

Cost	Average cost [(Min-Max) (Median)] (IDR)						$p^{\dagger}$
	a (IDR)	(%)	b (IDR)	(%)	c (IDR)	(%)	
Doctor services	150,000	28.4	150,000	25.4	150,000	29.6	1.00
CI (95%)							
Drug acquisition cost	115,566.38	21.9	178,782.27	30.2	94,944.00	18.7	0.00*
CI (95%)	(76,530-137,790) (119,310) 111,286.43 to 119,846.33		(155,310-210,060) (179,220) 172,889.45 to 184,675.09		(79,740-123,810) (88,050) 83,259.24 to 106,628.76		
Laboratory monitoring cost	262,340.43	49.7	262,727.27	44.4	262,000.00	51.7	0.89
CI (95%)	(190,000-270,000) (270,000) 257,066.33 to 267,614.52		(230,000-270,000) (270,000) 255,726.01 to 269,728.54		(190,000-270,000) (270,000) 243,902.74 to 280,097.26		
Total direct medical cost	528,019.57	100	591,509.55	100	506,944.00	100	0.00*
CI (95%)	(469.150-557.790) (531.810) 521,624.39 to 534,414.76		(556,760-630,060) (596,760) 583,007.96 to 600,011.13		(425,590-543,810) (508,050) 483,510.21 to 530,377.79		

a = (metformin + vildagliptin / sitagliptin + glimepiride), b = (metformin + vildagliptin / sitagliptin + pioglitazone), c = (metformin + glimepiride + pioglitazone), p >0.05 not significant, † uji kruskal-wallis, *significant, IDR = Indonesian Rupiah

Table 3. Baseline, endpoint, and change (Δ) in HbA1c across treatment combinations

	a	b	c	Total	$p^{\dagger}$
Average HbA1c baseline	7.2	6.57	7.31	7.03	0.14
(min-max) (median) (%)	(5.2 – 11.1) (7)	(5.2 – 9) (6.5)	(6.2 – 9.6) (6.7)	(5.2 – 11.1) (6.7)	
CI (95%)	6.80 to 7.59	6.21 to 6.93	6.40 to 8.22		
Average HbA1c endpoint	7.02	6.17	7.01	6.78	0.00*
(min-max) (median) (%)	(5 – 11) (6.8)	(4.7 - 6.9) (6.15)	(5.9 – 8.7) (6.9)	(4.7 – 11) (6.7)	
CI (95%)	6.66 to 7.38	5.90 to 6.44	6.30 to 7.71		
Average Δ HbA1c	0.17	0.40	0.30	0.25	0.69
(min-max) (median) (%)	(-2.9 - 3.6) (0.2)	(-0.6 - 2.1) (0.4)	(-0.6 - 1.9) (0.25)	(-2.9 - 3.6) (0.3)	
CI (95%)	-0.16 to 0.50	0.12 to 0.68	-0.23 to 0.83		

a = (metformin + vildagliptin / sitagliptin + glimepiride), b = (metformin + vildagliptin / sitagliptin + pioglitazone), c = (metformin + glimepiride + pioglitazone), † Kruskal-Wallis, p >0.05 not significant, *significant

Table 4. ACER and ICER from the base-case

Combination type	Average total direct medical cost (IDR)	Effectiveness (%)	ACER (IDR)	ICER (IDR)
a	528,019.57	0.17	3,069,881.22	-162,119.77
b	591,509.55	0.40	1,478,773.87	845,655.50
c	506,944.00	0.30	1,689,813.33	

a = (metformin + vildagliptin / sitagliptin + glimepiride), b = (metformin + vildagliptin / sitagliptin + pioglitazone), c = (metformin + glimepiride + pioglitazone), IDR = Indonesian Rupiah

combined with oral antidiabetic drugs. Because the Kruskal-Wallis test cannot be used for post hoc comparisons, the Mann-Whitney test is performed for each pair of groups to determine which groups differ. The results showed that both cost components differed significantly among the antidiabetic combinations (p <0.05).

Effectiveness of therapy

Treatment effectiveness was evaluated based on the reduction in HbA1c between baseline and follow-up measurements. Table 3 shows the baseline, endpoint, and change (Δ) in HbA1c across treatment combinations (metformin + sitagliptin / vildagliptin + glimepiride); (metformin + sitagliptin / vildagliptin + pioglitazone); and (metformin + glimepiride + pioglitazone), with an average difference in HbA1c baseline, HbA1c endpoint, and Δ HbA1c reduction of 7.03, 6.78, and 0.25, respectively. A difference test was then performed between the antidiabetic combinations and the HbA1c baseline, HbA1c endpoint, and Δ HbA1c reduction. The results showed no significant difference (p >0.05 in the Kruskal-Wallis test) for the HbA1c baseline and Δ HbA1c reduction, but there was a significant difference (p <0.05) for the HbA1c endpoint.

Cost-effectiveness analysis

Based on Table 4, the antidiabetic combination (metformin + sitagliptin / vildagliptin + glimepiride) has the highest ACER value compared to other antidiabetic combinations, which is IDR 3,069,881.22. Furthermore, the ICER value was calculated by comparing (metformin + glimepiride + pioglitazone) with (metformin + sitagliptin / vildagliptin + glimepiride) and (metformin + sitagliptin / vildagliptin + pioglitazone). The result was that the combination of Metformin + sitagliptin / vildagliptin + glimepiride and metformin + sitagliptin / vildagliptin + pioglitazone was more cost-effective, with ICER values of IDR -162,119.77; IDR 845,655.5, respectively.

Sensitivity analysis

We used a tornado diagram to depict the variables with the most significant impact on outcomes. The results of the one-way sensitivity analysis for the two comparisons showed different patterns in the factors that most influenced the ICER values. In the comparison of therapy combination (metformin + sitagliptin / vildagliptin + glimepiride) vs (metformin + glimepiride + pioglitazone), cost parameters,

especially primarily laboratory monitoring costs, were the most dominant factors influencing the results. In contrast, in the comparison of therapy combination (metformin + sitagliptin / vildagliptin + pioglitazone) vs (metformin + glimepiride + pioglitazone), effectiveness parameters, particularly ΔHbA1c in group (metformin + sitagliptin / vildagliptin + pioglitazone), were the most sensitive factors. Despite a ±20% variation across all parameters, the analysis results remained consistent, with therapy combination (metformin + sitagliptin / vildagliptin + glimepiride) being dominant compared to (metformin + glimepiride + pioglitazone). At the same time, the therapy combination (metformin + sitagliptin / vildagliptin + pioglitazone) demonstrated higher effectiveness but with the consequence of also greater costs compared to therapy (metformin + glimepiride + pioglitazone).

DISCUSSION

Most patients were classified under ICD-10 code E11.7 (T2DM with multiple complications), indicating at least one additional complication or comorbidity. The most prevalent comorbidities were related to the endocrine, metabolic, and cardiovascular systems, such as dyslipidemia and hypertension. This finding is consistent with the known association between T2DM, metabolic abnormalities, and increased cardiovascular risk.[10]

The cost of antidiabetic drugs is one of the contributors to the high total real direct medical costs. This is because the unit prices of pioglitazone and sitagliptin / vildagliptin are higher than those of glimepiride, resulting in increased total real direct medical costs. This finding is consistent with a UK study, which showed that the cost of metformin + TZD ($46,202) or metformin + DPP-4i ($47,191) was also higher than the cost of metformin + sulfonylurea ($40,669).[11] However, the high cost of the drugs must be weighed against the clinical benefits provided. Some literature suggests that pioglitazone and DPP-4i have a better safety profile than sulfonylureas, particularly regarding the risk of hypoglycemia and effects on cardiovascular function.[10]

Table 2 shows a significant difference in average drug costs and total direct medical costs between antidiabetic combinations, with a p <0.05, with the antidiabetic combination (metformin + sitagliptin / vildagliptin + pioglitazone) having the highest value. This suggests that the choice of therapeutic regimen will have a direct impact on the economic burden on both patients and healthcare facilities.

HbA1c is a surrogate marker that does not directly reflect long-term clinical outcomes; however, it remains a validated indicator of long-term glycemic control and is strongly associated with the risk of diabetes-related complications. Furthermore, HbA1c is a more practical measure than clinical outcomes, which take longer to be observed.[12]

HbA1c testing in this study was not performed routinely every three months, but rather at intervals ranging from three to nine months, depending on the patient's clinical condition. According to the literature, blood sugar monitoring can be conducted every 3-6 months, with 3 months recommended if the condition is uncontrolled and 6 months if it is controlled.[9] Additionally, all patients in this study utilized BPJS Kesehatan. According to the BPJS Kesehatan regulation, for type 2 DM patients, HbA1c testing is carried out with a frequency of once every 3 to 6 months.[13]

Table 3 shows the most significant Δ reduction in HbA1c in the antidiabetic combination containing pioglitazone. These results align with a study in Bulgaria, which showed that the combination containing pioglitazone was more effective in lowering HbA1c than DPP-4i.[14] Pioglitazone is known to be highly effective in reducing blood sugar, with A1C reductions of around 1.0% to 1.5%.[10] However, pioglitazone is not recommended for patients with heart failure because it can worsen edema or fluid retention. Therefore, the use of DPP-4i can be considered in patients with heart failure.[6]

The combination of metformin, sitagliptin / vildagliptin, and pioglitazone may be advantageous because each component acts through a distinct mechanism of action. Pioglitazone and metformin increase insulin sensitivity and improve β-cell function, with TZDs having a more prominent effect on β-cells. The characteristics of these two drugs make this combination suitable both as initial therapy and as adjunctive therapy in patients who do not achieve glycemic control targets.[14] At the same time, gliptins (sitagliptin or vildagliptin) do not affect insulin resistance. DPP-4i can reduce glucagon secretion, thereby improving the molar ratio of insulin to glucagon in the portal vein. This condition can reduce the hormonal stimulation of gluconeogenesis and glucose production in the liver. In addition, some experimental data suggest that DPP-4i can also directly affect glucose metabolism in the liver.[15]

The metformin + sitagliptin / vildagliptin + glimepiride regimen also demonstrated effectiveness in reducing HbA1c levels through complementary pharmacologic mechanisms. Sulfonylureas stimulate pancreatic β cells to release insulin, while metformin increases tissue sensitivity to insulin and improves glucose uptake.[10] Although the reduction in HbA1c obtained is relatively smaller compared to pioglitazone-based regimens. A study in Japan showed that the addition of sitagliptin to patients previously using metformin and sulfonylureas was able to provide a significant reduction in HbA1c, although not as large as the TZD-based combination.[16]

In this study, cost-effectiveness was analyzed by calculating ACER and ICER values. Table 4 shows that the antidiabetic combination (metformin + sitagliptin / vildagliptin + pioglitazone) had the lowest ACER value compared to the other two antidiabetic combinations, at IDR 1,478,773.87. Regarding the ICER calculation, (metformin + sitagliptin / vildagliptin + glimepiride) and (metformin + sitagliptin / vildagliptin + pioglitazone) was more cost effective than (metformin + glimepiride + pioglitazone) with ICER value

IDR -162,119.77; IDR 845,655.5, respectively. The ICER value is used to indicate the additional cost required to obtain one additional unit of health outcomes compared to other alternatives.[17]

The willingness to pay (WTP) threshold used in this study was 1 times Indonesia's GDP per capita (Int$14,445.7, which is equivalent to approximately IDR 220 million per unit of effectiveness).[9] When compared with the research results, all ICER values were well below this threshold. This indicates that the additional costs incurred are still within acceptable limits, thus the analyzed interventions can be considered cost-effective.

The analysis was conducted to determine the components and real direct medical costs in patients with type 2 diabetes. Cost calculations in this study did not include discounting, because the time period used was only one year. In a relatively short analysis period, the application of discounting to costs and outcomes is considered irrelevant, as changes in the value of money within one year do not yield a significant difference in the economic analysis.[18]

Limitations of the study

This study has several limitations. First, its retrospective design relied on the completeness and accuracy of routinely collected medical records. Second, despite total sampling, the treatment groups were uneven in size (Figure 2) which may have introduced selection bias. Third, information on medication adherence, duration of diabetes, dietary habits, smoking status, and physical activity was unavailable

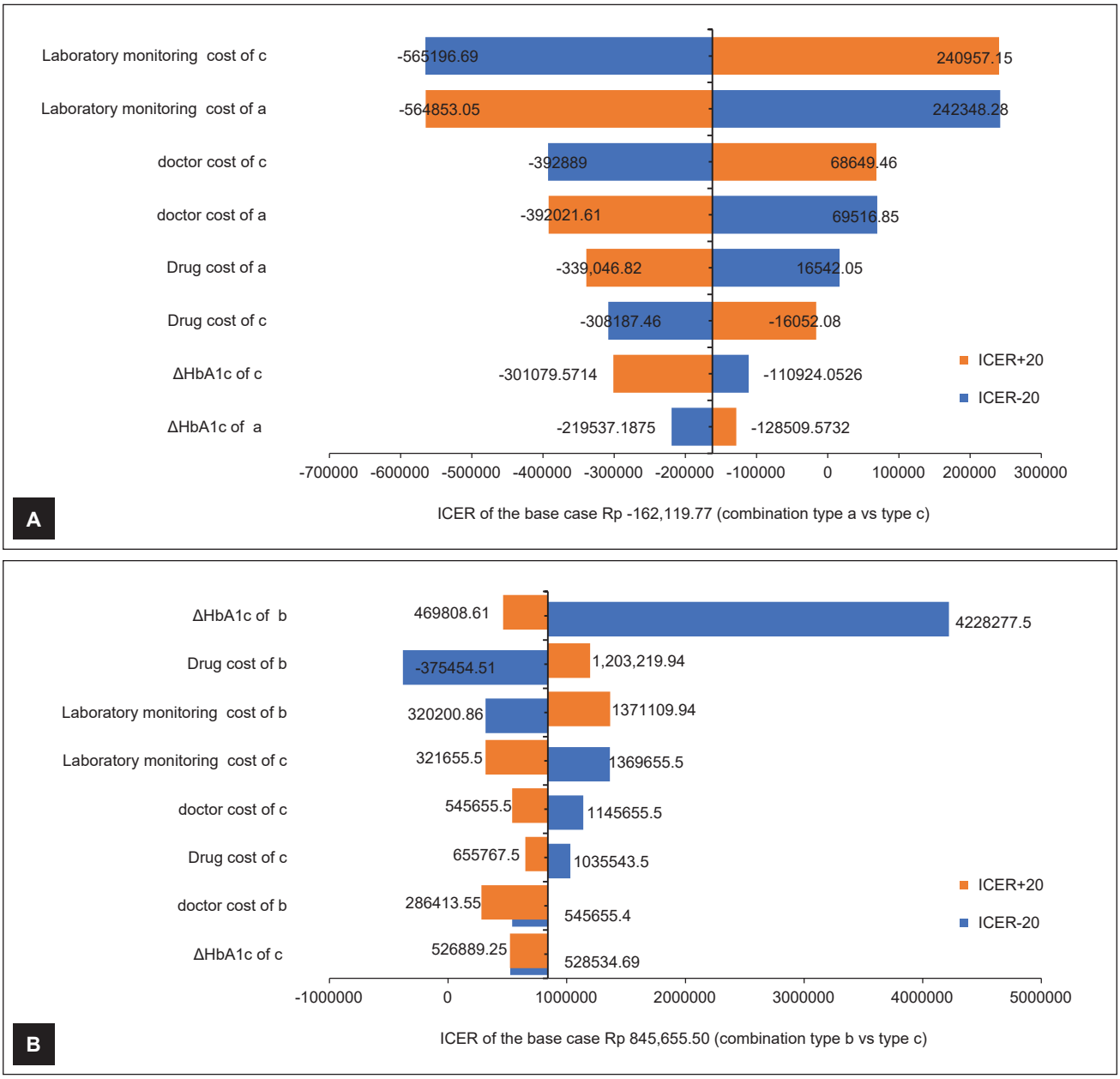

Figure 2. Tornado diagram showing the one-way sensitivity analysis. **(A)** Combination type a vs c. **(B)** Combination type b vs c.

and could not be evaluated as potential confounders. Fourth, HbA1c was used as the sole measure of effectiveness and may not fully capture long-term clinical outcomes such as complications, hospitalizations, or mortality. Finally, the one-year study period may not adequately reflect the long-term cost-effectiveness of the evaluated treatment regimens.

CONCLUSION

The combinations of metformin + sitagliptin / vildagliptin + glimepiride and metformin + sitagliptin / vildagliptin + pioglitazone were more cost-effective than metformin + glimepiride + pioglitazone from a hospital perspective. These findings may inform treatment selection among patients with T2DM needing triple oral antidiabetic therapy in tertiary care settings.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria

CRediT Author Statement
YN: Conceptualization, Methodology, Formal analysis, Data curation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **IAH:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **L:** Conceptualization, Validation, Formal analysis, Resources, Data curation, Writing – review and editing, Supervision, Project administration; **AR:** Validation, Investigation, Resources, Writing – review and editing, Supervision; **GNVA:** Methodology, Formal analysis, Data curation, Writing – review and editing, Visualization, Project administration, Funding acquisition.

Data Availability Statement
Datasets generated and analyzed are included in the published article.

Author Disclosure
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