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Cost-Effectiveness Analysis Of Metformin Use In Type 2 Diabetes Mellitus Patients In Hospitals: A Systematic Literature Review

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Abstract

Type 2 diabetes mellitus (T2DM) places a significant economic burden on Indonesia, necessitating the selection of cost-effective pharmacological therapies. Metformin has long been recommended as first-line therapy, but evidence of its cost-effectiveness across Indonesian hospitals remains fragmented and methodologically diverse. This study aimed to conduct a systematic review and synthesize evidence regarding the cost-effectiveness of metformin use in T2DM patients in Indonesian hospitals. The study used a systematic literature review design based on the PRISMA framework. Articles published since 2020 and obtained from Google Scholar, PubMed, and Publish or Perish were assessed using the PICO criteria (Population: T2DM patients in hospital; Intervention: metformin; other antidiabetic therapies; Outcome: cost-effectiveness). In total, six national studies were selected, covering both inpatient and outpatient settings. Data were extracted descriptively, while cost-effectiveness results (primarily the Average Cost-Effectiveness Ratio/ACER) were analyzed narratively. Across all reviewed studies, metformin consistently demonstrated lower ACER values than comparator therapies (e.g., glibenclamide, glimepiride, gliquidone, and acarbose-based combinations), suggesting better cost-efficiency with equivalent or higher clinical effectiveness. ***Conclusion:*** *Metformin is a cost-effective first-line therapy for T2DM patients in Indonesian hospitals, making it worthy of being maintained as the primary choice in clinical practice and hospital formularies.*

Keywords: Cost-effectiveness analysis, Hospital, Metformin, Type 2 diabetes mellitus.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) has become a complex and multidimensional global health crisis. According to a 2021 report by the International Diabetes Federation, the T2DM epidemic is showing an alarming trend, with prevalence increasing by 16% over the past decade, with an estimated 537 million adults currently living with the condition. This situation is even more challenging in developing countries like Indonesia, where data from the 2022 Basic Health Research (Riskesdas) revealed that the prevalence of T2DM reached 10.9% in the adult population, with early detection rates remaining low (Ministry of Health of the Republic of Indonesia, 2022). The economic impact of this disease is significant, with the annual cost of T2DM management in Indonesia estimated at IDR 25 trillion, including direct costs for medications, hospitalization, and complication management, as well as indirect costs due to lost productivity and family burden (PERKENI, 2021). Previous research also shows that the cost burden of DMT2 in Indonesia continues to increase, and the majority of costs are covered by the national health insurance system (Putri et al., 2020). This challenge is further complicated by disparities in access to optimal health services and therapy in various regions in Indonesia.

In the context of pharmacological therapy, metformin has maintained its position as first-line therapy for T2DM for over six decades. This recommendation is supported by strong evidence from various international clinical guidelines such as those from the American Diabetes Association (2023) and national organizations such as the Indonesian Endocrinology Society (PERKENI, 2021). Metformin's advantages lie not only in its effectiveness in lowering HbA1c levels by 1-2% (Rena et al., 2017), but also in its favorable safety profile with minimal risk of hypoglycemia and additional benefits such as mild weight loss. However, in the context of Indonesia's health system facing limited

resources and a high disease burden, cost-effectiveness considerations are a critical aspect that cannot be ignored. Furthermore, several meta-analyses have shown that metformin not only significantly lowers HbA1c but also has cardioprotective benefits and reduces the risk of cardiovascular mortality (Crowley et al., 2017). Cost-Effectiveness Analysis (CEA) is a systematic health economic evaluation method for comparing the costs and benefits of different types of health interventions (Drummondet.al, 2015). A comprehensive Cost-Effectiveness Analysis (CEA) is needed to quantitatively evaluate the trade-off between treatment costs and resulting clinical outcomes (Drummond et al., 2015). In global studies, CEA has become an important basis for budget allocation decisions, including for diabetes treatment (Tao et al., 2021). This approach has become increasingly relevant with the introduction of various new antidiabetic drugs that offer better clinical efficacy but are significantly more expensive than metformin.

Several studies in Indonesia have attempted to measure the cost-effectiveness of metformin in various clinical settings. A study by Ariawan et al. (2022) at Sukoharjo Regional General Hospital, which analyzed 62 inpatients, found that metformin therapy resulted in an Average Cost-Effectiveness Ratio (ACER) of IDR 31,132 per percent decrease in Random Blood Sugar (GDS), significantly lower than glibenclamide (IDR 44,280). Similar findings were reported by Marzuki et al. (2023) at Dr. Darsono Regional General Hospital in Pacitan, where metformin demonstrated superiority in both clinical effectiveness (86.84% vs. 74.07%) and cost efficiency (ACER IDR 4,177,076 vs. IDR 5,083,508) compared to glimepiride. However, the results of these studies are still fragmented with varying methodologies, such as differences in outcome parameters (GDS vs. HbA1c), observation periods, and calculated cost components. In addition, existing studies tend to be limited to specific hospital settings without considering variations in patient characteristics and clinical practice patterns in various regions in Indonesia..

Based on this background, this systematic literature review is designed to provide a comprehensive and critical synthesis of the existing evidence regarding the cost-effectiveness of metformin in patients with T2DM in Indonesian hospitals. Specifically, this study aims to: (1) conduct a comparative analysis of the cost-effectiveness parameters (ACER, ICER) of metformin versus alternative therapies based on existing studies; (2) evaluate the consistency of metformin cost-effectiveness findings across hospital settings and patient populations; (3) identify factors influencing variations in cost-effectiveness results across studies; and (4) formulate evidence-based policy recommendations for optimizing resource allocation in hospitals. With this systematic and critical approach, the literature review is expected to not only provide academic contributions but also serve as a basis for more evidence-based clinical decision-making and health policy in Indonesia.

RESEARCH METHODS

Data Search Strategy

This study uses the systematic literature review (SLR) method, which is a type of research method by collecting information from scientific articles with relevant discussions, then evaluating the information and data, processing the information and data to interpreting the information and data that have been obtained from scientific articles. Systematic literature review is a medium for summarizing related information obtained from articles or other scientific sources through the process of searching, selecting, and synthesizing literature studies. In writing this article, the keywords used are "Cost-effectiveness analysis" AND "Metformin Therapy" AND "Metformin Drug" AND "Type 2 Diabetes" AND "Hospital" AND "Cost Effectiveness Analysis" AND "Metformin" AND "Metformin Therapy" AND "Type 2 Diabetes" AND "Hospital"

Resources

In the process of searching for related literature studies, the author used digital platforms, namely Google Scholar, PubMed and Publish or Perish.

Eligibility Criteria

The eligibility criteria in this article include inclusion criteria and exclusion criteria. The inclusion criteria set in writing this article include: 1) scientific literature sources are scientific journals, 2) scientific sources originating from the Google Scholar, PubMed and Publish or Perish platforms, 3) Scientific journals that have free or open access to the public, 4) Scientific journals in Indonesian or English, 5) Scientific journals published at least in 2020, 6) Scientific journals with at least a discussion on the cost-effectiveness of metformin use in type 2 diabetes patients in hospitals. Meanwhile, the exclusion criteria in writing this article are all criteria that are not included in the inclusion criteria. In an effort to limit the scope of the study, the author used the PICO method (Population/Problem, Intervention, Comparison, Outcomes).

Table 1. PICO Summary

Element	Information
Population	Patient with type 2 diabetes in hospital, Patient with type 2 diabetes indicate in hospital
Intervention	Use of metformin medication/therapy
Comparison	Use of therapy or medication for type 2 diabetes patients
Outcomes	Cost-effectiveness

In conducting the literature selection, the author also used the PRISMA (Preferred Reporting Items For Systematic Review and Meta-analysis) method. PRISMA is a method for compiling, reporting, and evaluating systematic reviews and meta-analyses. The PRISMA method ensures that research results are transparent, complete, and replicable. The PRISMA method is presented through a flowchart explaining the writing process for this article, starting with identification, screening, eligibility, and inclusion.

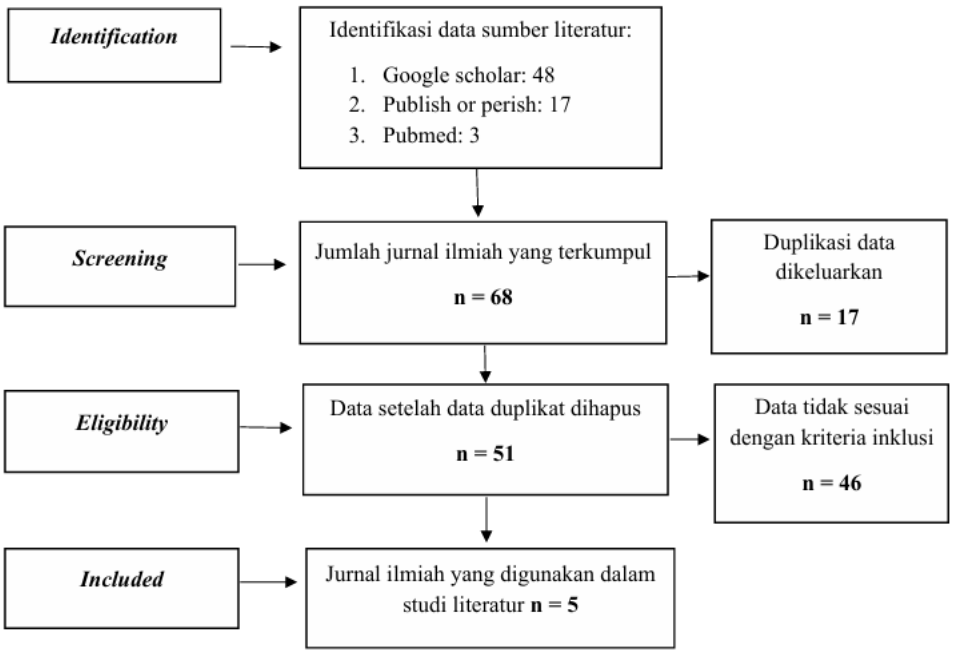

Figure 1. Prism Diagram

RESULTS AND DISCUSSION

Results

Table 2. Literature Extraction Results

Author/Year	Title	Method	Results
Marzuki,et.al, 20220	Cost-Effectiveness Analysis of Metformin and Glimperide Therapy in Type 2 Diabetes Mellitus Patients at Dr. Darsono Regional Hospital, Pacitan, in 2019	descriptive-observational research with a cross-sectional design.	Metformin therapy was more effective than glimepiride in managing type 2 diabetes in inpatients at Dr. Darsono Pacitan Regional Hospital in 2019. The effectiveness percentage of metformin therapy was 86.84%, while glimepiride was 74.07%. In terms of costs, the average total cost of metformin therapy was Rp 3,627,373, lower than glimepiride's Rp 3,765,355. Cost-Effectiveness analysis shows that metformin has a lower Average Cost-Effectiveness Ratio (ACER) of IDR 4,177,076 compared to glimepiride which reached IDR 5,083,508, indicating that metformin is more cost-effective.
Wuryandari,et.al. 2021	Cost-Effectiveness Analysis of Combination Oral Antidiabetic Therapy in Type 2 Diabetes Mellitus Patients at Madiun City Hospital in 2020	non-experimental research with a descriptive design through secondary data tracing in the form of cross-sectional medical records.	The results of the study showed that drug therapy A (a combination of metformin and glimepiride) had a higher effectiveness of 98% compared to drug therapy B (metformin and acarbose) which was 94%. The average cost of treatment for drug A was Rp 4,676,823, - lower than drug B which was Rp 5,302,005, -. From the cost-effectiveness analysis using ACER (Average Cost Effectiveness Ratio), the ACER value of drug A was

Author/Year	Title	Method	Results
			Rp 47,722, - lower than drug B which was Rp 56,404, -, so drug therapy A was considered more cost-effective and included in the dominant category.
Hadiq,et.al. 2022	Cost-Effectiveness Analysis of Metformin and Metformin-Glimperide in Patients With Type 2 Diabetes at Nene Mallomo General Hospital, Sidenrang Rappang	Cost-effectiveness analysis in patients with type 2 diabetes mellitus. Data were collected from patient medical records and the hospital management information system using a data collection form. Quantitative	Metformin monotherapy is more cost-effective than metformin-glimepiride combination therapy in patients with type 2 diabetes mellitus at Nene Mallomo General Hospital. Quantitatively, the effectiveness of metformin monotherapy is 64.29% with a total direct treatment cost of IDR 120,736, resulting in an ACER of 1877.99 per % of therapy effectiveness. Meanwhile, metformin-glimepiride combination therapy has an effectiveness of 62.50% with a total cost of IDR 126,298, resulting in an ACER of 2020.77 per % of therapy effectiveness.
Meliawati,et.al. 2023	Cost-Effectiveness Analysis of The Use of Metformin and Glimperide in Patients With Type 2 Diabetes Mellitus Inpatient at The Hospital Robbert Wolter Mongisidi Manado City	non-experimental observational research with a descriptive design.	Based on the Average Cost-Effectiveness Ratio (ACER) calculation, metformin therapy has an ACER value of Rp 49,156, while glimepiride therapy has an ACER value of Rp 73,718. Because a smaller ACER value indicates a more cost-effective therapy, metformin is considered a more cost-effective therapy for the treatment of type 2 diabetes mellitus at Robert Wolter Mongisidi Hospital, Manado City.

Author/Year	Title	Method	Results
Widia Wiwin, Liska Marlinda. 2021	Cost and Effectiveness Analysis of the Use of Metmorphine and Gliquidone in Type 2 Diabetes Mellitus Patients in the Outpatient Installation of Hospital X, 2020 Period	Calculate the comparison of the effectiveness of therapy results and the cost-effectiveness of metformin and gliquidone therapy in outpatients with type 2 diabetes mellitus at Hospital X, using the Average Cost-Effectiveness Ratio (ACER) method based on CEA. 24 medical records of patients who met the criteria were taken as research samples.	Metformin has an ACER of Rp. 3,393, which is lower than gliquidone's Rp. 3,710, indicating that metformin's cost per unit of effectiveness is more efficient. Metformin's effectiveness was recorded at 89%, indicating that the majority of patients successfully achieved their target random blood sugar levels.

DISCUSSION

Comparison of Cost-Effectiveness Parameters (ACER and ICER)

Cost-effectiveness analysis in pharmacoeconomic studies relies on two main indicators: the Average Cost-Effectiveness Ratio (ACER) and the Incremental Cost-Effectiveness Ratio (ICER). Both are used to evaluate how much money is spent for each unit of effectiveness achieved by a therapeutic intervention. ACER is used to calculate the ratio of total costs to total effectiveness in a single treatment group, while ICER compares the efficiency of two different therapies based on the difference in cost and effectiveness between them. Of the six studies reviewed, all showed that metformin therapy consistently produced lower ACER values than its alternative therapies, both as monotherapy and combination therapy. In a study in the United States, for example, metformin had the lowest cost-effectiveness ratio compared to sulfonylureas and insulin in a 10-year simulation model (CDC, 2018). A study at Sukoharjo Regional Hospital noted that the ACER for metformin was Rp 31,132, while glibenclamide reached Rp 44,280. In this context, the ACER calculation indicates that every one percent increase in therapeutic effectiveness with metformin costs less than with glibenclamide. Therapeutic effectiveness is measured by the proportion of patients achieving target blood glucose control (BGs), and metformin has been shown to be superior in both cost and clinical outcomes.

Similar findings emerged in a study at Dr. Darsono Pacitan Regional Hospital comparing metformin with glimepiride. The ACER value for metformin therapy was Rp 4,177,076, lower than that for glimepiride, which reached Rp 5,083,508. This means that although the difference in total costs between the two therapies is not very significant (around Rp 138,000), metformin remains more efficient in terms of cost per unit of effectiveness. The effectiveness of the therapy was measured based on the reduction in fasting blood glucose (FBG), with the results that metformin was 86.84% effective compared to glimepiride at 74.07%. This shows that a nominally cheaper therapy does not

always mean more efficient; efficiency is determined by the comparison between costs and clinical outcomes.

One study examining the combination of antidiabetic therapy was conducted at Madiun City Hospital.In this study, the combination of metformin and glimepiride was 98% effective at an average cost of Rp 4,676,823, resulting in an ACER of Rp 47,722. Meanwhile, the combination of metformin and acarbose was 94% effective at a higher cost (Rp 5,302,005) and an ACER of Rp 56,404. Because metformin–glimepiride was more effective and less expensive, it was considered dominant, and in such cases, an ICER calculation was not necessary. This is in line with the principle that an ICER should only be calculated when one therapy is more expensive but also more effective, or less expensive but less effective.

However, a different study at Nene Mallomo Sidenreng Rappang Regional Hospital revealed a different perspective. There, metformin alone was compared with a metformin-glimepiride combination. The results showed that metformin alone had an ACER of Rp 1,877.99 per unit.effectiveness, lower than the combination, which reached Rp 2,020.77. Although the effectiveness of the two therapies was relatively close (64.29% vs. 62.50%), the difference in cost and effectiveness was not large enough to declare absolute dominance, making the ICER analysis more relevant. However, this study chose to continue presenting the results in the form of ACER, which is sufficient to demonstrate the economic superiority of metformin. Interestingly, in the outpatient study at Hospital X, although the effectiveness of gliquidone (100%) was higher than that of metformin (89%), the ACER of metformin (Rp 3,393) was still lower than that of gliquidone (Rp 3,710). This indicates that metformin remains more cost-effective per unit of effectiveness, although not the most effective in absolute terms.

Meanwhile, a study at Robert Wolter Monginsidi Hospital in Manado also confirmed the consistency of metformin as a therapy.*cost-effective*. The ACER for metformin of Rp 49,156 is significantly lower than that for glimepiride of Rp 73,718. In this context, the cost to achieve one unit of therapeutic success with glimepiride is almost 1.5 times that of metformin. From these overall results, it can be concluded that the ACER is a fairly informative measure for assessing the relative efficiency between various antidiabetic therapies, especially when the difference in effectiveness is not too large. However, for cases where effectiveness and costs are significantly different but do not show a clear dominance, the ICER is crucial for determining whether the increase in effectiveness of a therapy is indeed worth the increase in cost.

Consistency of Metformin Cost-Effectiveness Findings in Type 2 Diabetes Patients in Hospitals

One of the primary objectives of this literature review is to evaluate the extent to which the cost-effectiveness findings of metformin use in patients with type 2 diabetes mellitus are consistent across hospitals and patient settings. Consistent results are important to ensure that recommendations for metformin use are broadly applicable and not limited to specific contexts or regions. Based on the six studies reviewed, the findings regarding metformin's cost-effectiveness demonstrate a high degree of consistency, despite some variation in effectiveness measures and cost figures. In general, metformin consistently emerged as a more cost-effective therapy than comparator therapies, both as monotherapy and in combination. This consistency can be seen in the results from hospitals in various regions, such as Sukoharjo Regional General Hospital (Central Java), Dr. Darsono Regional General Hospital (Pacitan) (East Java), Madiun City Regional General Hospital (Parliament), Nene Mallomo Regional General Hospital (South Sulawesi), Robert Wolter Monginsidi Hospital (North Sulawesi), and private hospitals in other regions. The findings of each study, while differing in methodological aspects, nevertheless show a similar pattern: the total cost of metformin is lower or equivalent to alternative therapies, while its effectiveness is at least comparable, and in many cases even higher.

For example, at Sukoharjo Regional Hospital, metformin was not only less expensive than glibenclamide but also demonstrated superior therapeutic efficacy. At Pacitan Regional Hospital, this

pattern recurred, with metformin yielding a lower cost-effectiveness ratio (ACER) than glimepiride, despite a slight difference in clinical effectiveness. A study at Madiun City Hospital showed that metformin combined with glimepiride provided superior results in terms of effectiveness and cost. Even when compared with gliquidone, which was slightly more clinically effective (100% vs. 89%), metformin was still considered more cost-effective due to its lower cost-effectiveness, as demonstrated in an outpatient study at Hospital X. These consistent findings apply not only to inpatient populations but also to more diverse settings, such as outpatient and short-term care, and among patients with various demographic profiles, including those aged 40–80 years. This consistency suggests that metformin can be a stable and reliable approach in the management of type 2 diabetes, both clinically and economically.

In the context of cost-effectiveness consistency, it is important to emphasize that although the absolute values of costs and effectiveness differed across hospitals, the ratio between the two still indicated metformin's superiority. This means that differences in service rates, drug prices, or intensity of resource use did not alter the primary conclusion that metformin is a more cost-effective therapy. This strengthens the external validity of the findings and supports the use of metformin as the primary therapy of choice in standard care for type 2 diabetes across various hospital settings. However, some variations still emerged. For example, in a study at Nene Mallomo Regional Hospital, the effectiveness of metformin as monotherapy was only slightly higher than that of the metformin-glimepiride combination. Nevertheless, the ACER for metformin remained lower, indicating that this single therapy remained more cost-effective. This demonstrates that consistency does not mean absolute uniformity, but rather the stability of the core findings, in this case, the dominance of metformin's cost-efficiency amid differences in parameters and clinical conditions across studies.

Factors Affecting Variation in Cost-Effectiveness Results of Metformin Use in Type 2 Diabetes Patients in Hospitals

Although metformin has generally been shown to be more cost-effective than other antidiabetic therapies, there is variation between studies in terms of therapeutic effectiveness, total costs, and ACER values. This variation is due to several important factors, such as study design, patient characteristics, inclusion and exclusion criteria, effectiveness indicators, and hospital cost structures.

First, differences in effectiveness measurement methods are a significant source of variation. In some studies, such as those at Sukoharjo Regional General Hospital and Dr. Darsono Regional General Hospital in Pacitan, effectiveness was measured based on random blood glucose (GDS) or fasting blood glucose (FBG). Meanwhile, other studies, such as those at Madiun City Regional General Hospital, defined effectiveness as the patient's success in achieving a specific clinical condition based on a combination of parameters, such as glucose levels and discharge status (recovered and discharged).

Second, the characteristics of the patient population in each study significantly influenced the cost-effectiveness results. For example, at Dr. Darsono Pacitan Regional Hospital, the study restricted patient age to 45–80 years and included only patients without complications. This restriction allowed the metformin effectiveness results to appear higher because more clinically stable patients tend to respond better to therapy. In contrast, the study at Nene Mallomo Regional Hospital did not specify age but included new patients without comorbidities, who may have different metabolic characteristics.

Third, the inclusion and exclusion criteria used in sampling also have a significant impact. In the study at Robert Wolter Monginsidi Hospital in Manado, for example, only patients with a GDP between 250–350 mg/dL were included, as well as patients aged 40–60 years without comorbidities. This rigorous sample selection tends to result in higher effectiveness because it involves only patients with homogeneous and relatively stable characteristics. This contrasts with the outpatient study at

Hospital X, where patient clinical variability may be higher because external factors such as patient compliance, diet, and physical activity are not as stringently controlled as in inpatient settings. As a result, the effectiveness of metformin at Hospital X was still high (89%), but not as high as in other inpatient studies, and the total cost of treatment was also higher.

Fourth, the structure and rates of hospital fees are also important factors. While the prices of generic drugs like metformin are relatively uniform nationally, other components of total direct medical costs, such as doctor visits, laboratory tests, hospitalization, and facility use, can vary significantly between hospitals. For example, the average cost of metformin therapy at Pacitan Regional General Hospital (Rp 3.6 million) is higher than at Sukoharjo Regional General Hospital (Rp 2.8 million), despite only a small difference in effectiveness. This suggests that the composition of costs within the hospital system plays a significant role in determining the final ACER value, and strengthens the argument that cost-effectiveness evaluations should consider all medical costs comprehensively, not just drug prices.

Fifth, the complexity of therapy and the type of comparator also influence the results. In studies at Madiun City Hospital and Nene Mallomo Hospital, combination therapy (e.g., metformin-glimepiride) was compared with monotherapy or other combinations (e.g., metformin-acarbose). Combination therapy certainly increases costs directly, but does not necessarily increase effectiveness proportionally. The Nene Mallomo study showed that although the metformin-glimepiride combination was slightly cheaper than monotherapy, its effectiveness was lower, so metformin alone remained more cost-effective. This suggests that adding a drug does not automatically increase cost-effectiveness, especially if the addition does not provide meaningful clinical improvement.

CONCLUSION

This systematic literature review found that the use of metformin in patients with type 2 diabetes mellitus in Indonesian hospitals consistently demonstrated better cost-efficiency than a number of comparator therapies, both as monotherapy and in combination. Across the studies analyzed, metformin therapy generally resulted in lower Average Cost-Effectiveness Ratio (ACER) values while achieving equivalent or even higher therapeutic effectiveness, thus making metformin a more cost-effective option per clinical unit. This consistency was evident across hospital types and service settings, both inpatient and outpatient, despite variations in effectiveness indicators, cost components, patient characteristics, and service fee structures across hospitals. These findings reinforce metformin's position as a first-line therapy that is not only clinically effective but also efficient in the context of the economic burden of diabetes mellitus in Indonesia.

As a literature review, the main limitations of this study lie in the heterogeneity of methodology and outcome criteria across studies, making it difficult to conduct quantitative meta-analyses or uniform absolute comparisons. Furthermore, the majority of studies are retrospective with secondary medical record data, making them vulnerable to selection bias and limited completeness of long-term cost and outcome data. Future research requires more methodologically homogeneous cost-effectiveness studies, with a clear perspective (e.g., health system or BPJS), consistent clinical outcome indicators (e.g., changes in HbA1c), and involving various levels of health facilities and insurance classes. Practical implications of this study include the need to integrate evidence of metformin's cost-effectiveness into clinical guidelines and hospital formularies, routine monitoring of the cost-effectiveness of type 2 diabetes therapy through synergy between clinical pharmacy, medical records, and hospital management, and strengthening electronic medical record-based reporting systems to support more evidence-based resource allocation decisions in an era of increasingly limited national health funding.

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