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Aspirin-clopidogrel combination therapy for ischemic stroke patients: Clinical efficacy and cost-effectiveness analyses in low-resource setting

Najmiatul Fitria[1*], Dian Febiana[2], Muhammad Akram[3] and Rahmi Yosmar[1]

[1]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Andalas, Padang, Indonesia; [2]Faculty of Pharmacy, Universitas Andalas, Padang, Indonesia; [3]Department of Eastern Medicine, Government College University, Faisalabad, Pakistan

*Corresponding author: najmiatulfitria@phar.unand.ac.id

Abstract

Understanding the cost-effectiveness of aspirin-clopidogrel combination therapy is crucial in determining its influence on coagulation parameters, specifically prothrombin time (PT) and activated partial thromboplastin time (APTT). The aim of this study was to assess the cost-effectiveness and clinical impact of using the aspirin-clopidogrel combination compared to aspirin alone in managing ischemic stroke. Employing an observational research design, inpatient ischemic stroke cases receiving the aspirin-clopidogrel combination were compared to those treated with aspirin alone. Focusing on the hospital's perspective on costs, the research specifically analyzed medical expenses without discounting costs or effects. The analysis involved comparing the direct medical costs and coagulation parameters between the two treatment groups. Our data revealed that the aspirin-clopidogrel combination demonstrated superior cost-effectiveness over aspirin alone, indicated by the incremental cost-effectiveness ratio (ICER) values for PT (IDR -246,930/second) and APTT (IDR -119,270/second). This indicated that the combination therapy was associated with lower costs while yielding better clinical parameter values. The ICER analysis placed the aspirin-clopidogrel combination in the southeast quadrant, marking its dominance over aspirin monotherapy by demonstrating higher effectiveness at lower costs. These results suggest that combination therapy might be a favorable alternative for managing ischemic stroke, presenting a viable option for consideration in clinical practice. The findings underscore the potential economic and clinical advantages of employing the aspirin-clopidogrel combination in routine stroke management protocols.

Keywords: Stroke, aspirin, clopidogrel, cost-effectiveness, ICER

Introduction

Ischemic stroke remains a significant global health concern, contributing to substantial morbidity, mortality, and economic burden [1,2]. Among the various therapeutic approaches, antiplatelet therapy has long been a cornerstone in preventing recurrent ischemic events. Aspirin, a widely used antiplatelet agent, has effectively reduced the risk of secondary stroke [1,3]. However, recent attention has turned towards combination therapy, particularly using aspirin in conjunction with clopidogrel, aiming to enhance antiplatelet effects and potentially improve patient outcomes [4-6].

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The Global Burden of Disease studies have estimated that in 2017, there were approximately 24.1 million new cases of stroke, 15.7 million more disability-adjusted life years (DALYs), and 700,000 more stroke-related deaths compared to the previous year [7]. In Indonesia, the proportion of people affected by stroke has risen from 0.7% in 2013 to 1.09% in 2018 [8]. This increase in the prevalence of cardiovascular disease has led to a higher number of outpatient and inpatient services, as well as an economic impact that the state must manage through the National Health Insurance Program [9]. According to the Social Security Agency, stroke costs a significant service fee [10], leading to a significant disease burden [11,12]. Apart from medical expenses, people with cardiovascular disease will cause economic losses to the country's productivity [13].

The rationale behind this investigation lies in the dual significance of clinical efficacy and economic feasibility. Ischemic stroke management involves a delicate balance between achieving therapeutic benefits and considering the economic impact on patients, healthcare providers, and society at large. As such, understanding the cost-effectiveness of employing aspirin-clopidogrel becomes pivotal, given its potential to influence coagulation, an essential aspect of stroke management. Assessing coagulation parameters—such as prothrombin time (PT) and activated partial thromboplastin time (APTT) [14,15]—this study aimed to elucidate the impact of this combination therapy on these crucial markers, which directly influence the clotting cascade [16-18].

Moreover, the economic aspect of the analysis is equally vital. Cost-effectiveness analysis (CEA) serves as the guiding framework, enabling the comparison of both costs and outcomes associated with alternative therapeutic interventions [19]. By conducting a rigorous CEA, we intend to shed light on the economic implications of implementing the aspirin-clopidogrel combination in routine clinical practice, specifically focusing on its influence on coagulation parameters (PT and APTT) among ischemic stroke patients [4,20,21].

Methods

Research design, target population

The study was carried out at Dr. M. Djamil Hospital, Padang, Indonesia, in 2023. It employed an observational research design that involved the assessment of records of hospitalized patients with ischemic strokes. The purposive sampling was used to select 97 patients for in-depth analysis. This study was a study-based health economics evaluation through retrospective data. In this study, we referred to the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) checklist [22,23].

Inclusion and exclusion criteria

The study enrolled Social Insurance Administration Organization (BPJS) insured hospitalized patients diagnosed with ischemic stroke, aged over 18, receiving aspirin-clopidogrel combination or aspirin alone, and had coagulation parameters assessments (PT and APTT) and medical cost data. Those who passed away during treatment were excluded.

Perspective, time horizon, and index year

This study adopted the hospital's perspective regarding costs, focusing on medical expenses paid to the hospital. The samples consisted of BPJS-registered patients diagnosed with ischemic stroke between January and December 2021, meeting specific criteria. The analysis spanned a year, with 2021 as the index year, establishing the time horizon for the research.

Currency and discount rate

The Indonesian Rupiah (IDR) was the currency utilized in this study. As it operated within the same fiscal year, no adjustments for discounted costs or effects were implemented [19,24].

Cost-effect variables

The expenses considered were specific direct medical costs encompassing administrative, inpatient, supportive, and medication expenses extracted from the Hospital Information and Management System (SIMRS). Additionally, the influential factors/effect parameters analyzed depend on coagulation elements, which were PT and APTT [5,17,18].

Data analysis

Data analysis started by calculating effectiveness based on therapy results, initial values before treatment, and after treatment on the PT and APTT values. For each dependent variable (total direct cost, PT and APTT values), a normality test was carried out first. The data were analysed using the Mann-Whitney or Chi-squared test as appropriate [25]. The result of a $p<0.05$ is declared to have a significant effect. Next, a cost-effectiveness analysis was carried out by calculating the incremental cost-effectiveness ratio (ICER) value, both PT and APTT, as explained previously [26], with the total direct cost as the cost parameter and PT-APTT as the effect parameter. ICER of PT was obtained by dividing the incremental cost of the single and combination therapy groups by the incremental PT values of the single aspirin and combination therapy groups. Likewise, the ICER of APTT was also calculated by dividing the incremental cost of the single and combination groups by the incremental APPT values of the single and combination groups.

Sensitivity analysis

A tornado diagram was used to describe the deterministic sensitivity analysis to evaluate the impact of varying input parameters on a model's output. The process started with identifying parameters, including cost, PT, and APTT value. From all these parameters, the ICER were obtained. Next, the sensitivity was calculated due to changes in prices and costs from the ICER using a tornado diagram. The estimated range for each parameter tested was 20% [27]. This number gives a range of assumptions adjusted by up to 20% (80–120%) of each ICER parameter. This number depicted how those changes would affect the outcome of the model. The actual ICER, which is obtained from the equation, would be the reference value [27-29].

Results

Sociodemographic and clinical characteristics

In this study, there were 216 patients diagnosed with ischemic stroke in 2021; however, only 97 patients met the inclusion criteria. Of the 97 patients, 48 patients used aspirin alone, and 49 patients used a combination of aspirin and clopidogrel. The sociodemographic characteristics of the patients are presented in **Table 1**. The sample size was relatively small because patients treated with aspirin and clopidogrel were limited, and some patients had a switch of therapy. Our analyses indicated that there was no association between age, gender, educational attainment, and occupation with the selected antiplatelet treatment (all had $p>0.05$), indicating no significant difference between single and combination therapy groups.

Table 1. Sociodemographic and clinical characteristics of ischemic stroke patients included in the study (n=97)

Sociodemographic characteristics	Aspirin (n=48)		Aspirin-clopidogrel combination (n=49)		All patients (n=97)		*p*-value
	n	%	n	%	n	%	
Age (year), mean±SD	59.1±10.1		56.6±10.7		57.8±10.4		0.264[a]
25–34	0	0.0	3	6.1	3	3.1	0.320[b]
35–44	2	4.2	4	8.2	6	6.2	
45–54	12	25.0	8	16.3	20	20.6	
55–64	22	45.8	23	46.9	45	46.4	
65–75	9	18.8	9	18.4	18	18.6	
>75	3	6.3	2	4.1	5	5.2	
Gender							0.480[b]
Male	23	47.9	28	57.1	51	52.6	
Female	25	52.1	21	42.9	46	47.4	
Educational attainment							0.313[b]
Low	7	14.6	6	12.0	13	13.4	
Middle	31	64.6	26	53.1	57	58.8	
High	10	20.8	17	34.7	27	27.8	
Occupation							0.619[b]
Working	20	41.7	17	34.7	37	38.1	
Not working	28	58.3	32	65.3	60	61.9	

Sociodemographic characteristics	Aspirin (n=48)		Aspirin-clopidogrel combination (n=49)		All patients (n=97)		*p*-value
	n	%	n	%	n	%	
Underlying disease							0.068[b]
Hypertension	15	31.3	9	18.4	24	24.7	
Diabetes mellitus	3	6.3	1	2.0	4	4.1	
Dyslipidemia	1	2.1	5	10.2	6	6.2	
Hypertension+ diabetes mellitus	13	27.1	8	16.3	21	21.6	
Hypertension+ dyslipidemia	3	6.3	11	22.4	14	14.4	
Diabetes mellitus + dyslipidemia	4	8.3	4	8.2	8	8.2	
Others	9	18.8	11	22.4	20	20.6	

[a] Analysed using Mann-Whitney
[b] Analysed using Chi-squared test

Chi-squared test statistical analysis was also carried out to determine the relationship between the two groups, with the complications using the Chi-Squared test (**Table 1**). The data suggested no association between underlying disease and the type of antiplatelet received (*p*=0.068). In the single aspirin group, patients with hypertension had a higher proportion compared to other underlying diseases, whereas in the aspirin-clopidogrel combination group, the highest proportion was hypertension with dyslipidemia and other complications (**Table 1**).

Effectiveness of aspirin single and combination aspirin-clopidogrel therapy in ischemic stroke patients

The effectiveness of using aspirin and the combination of aspirin with clopidogrel can be seen in **Table 2**. When examining the PT value, it was obtained that *p*=0.014 with Mann-Whitney statistical analysis, which means that there is a significant difference between the two types of antiplatelet received and the effectiveness value in the difference in PT value. So, it can be seen that the type of antiplatelet given to the patient, either in combination or alone, influences the value of the patient's effectiveness parameter in the difference in PT values.

Table 2. Effectiveness of aspirin single and combination aspirin-clopidogrel therapy in ischemic stroke patients

Effect parameters	Aspirin			Aspirin-clopidogrel			*p*-value
	Mean±SD	95%Cl		Mean±SD	95%Cl		
		Lower	Upper		Lower	Upper	
Difference of PT	2.05±2.96	1.19	2.91	4.04±5.50	2.46	5.62	0.014[a*]
Difference of APTT	3.14±2.80	2.33	3.96	7.26±22.32	0.85	3.67	0.194[a]

APTT: activated partial thromboplastin time; PT: prothrombin time
[a] Analysed using Mann-Whitney
[*] Significant at *p*<0.05

Table 3. The incremental cost-effectiveness ratio on prothrombin time (PT) and activated partial thromboplastin time (APTT)

Antiplatelet types	Direct medical cost (IDR)	Average difference in PT values (second)	Average difference in APTT values (second)	ICER PT (IDR/second)	ICER APTT (IDR/second)
Aspirin	11,109,062	2.05	3.14	-246,930	-119,270
Aspirin-clopidogrel	10,617,671	4.04	7.26		

The ICER value for the PT and APTT, calculated by comparing the difference between the average direct medical costs and the difference between the average PT and APTT values between the aspirin-clopidogrel combination intervention group and aspirin alone are presented in **Table 3**. In this study, an ICER value of IDR -246,930 was obtained for every one second decrease in PT value compared to a single aspirin. The cost-effectiveness plane of PT using aspirin and aspirin-clopidogrel combination is presented in **Figure 1** while the cost-effectiveness plane of APTT using aspirin and aspirin-clopidogrel combination is presented in **Figure 2**.

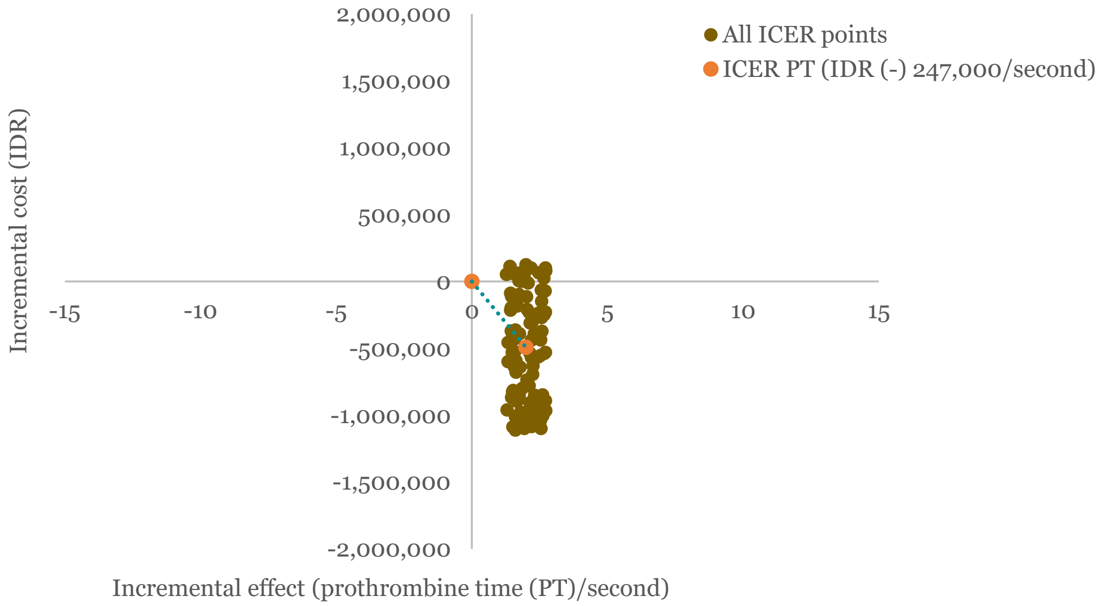

Figure 1. Cost-effectiveness plane of prothrombin time (PT).

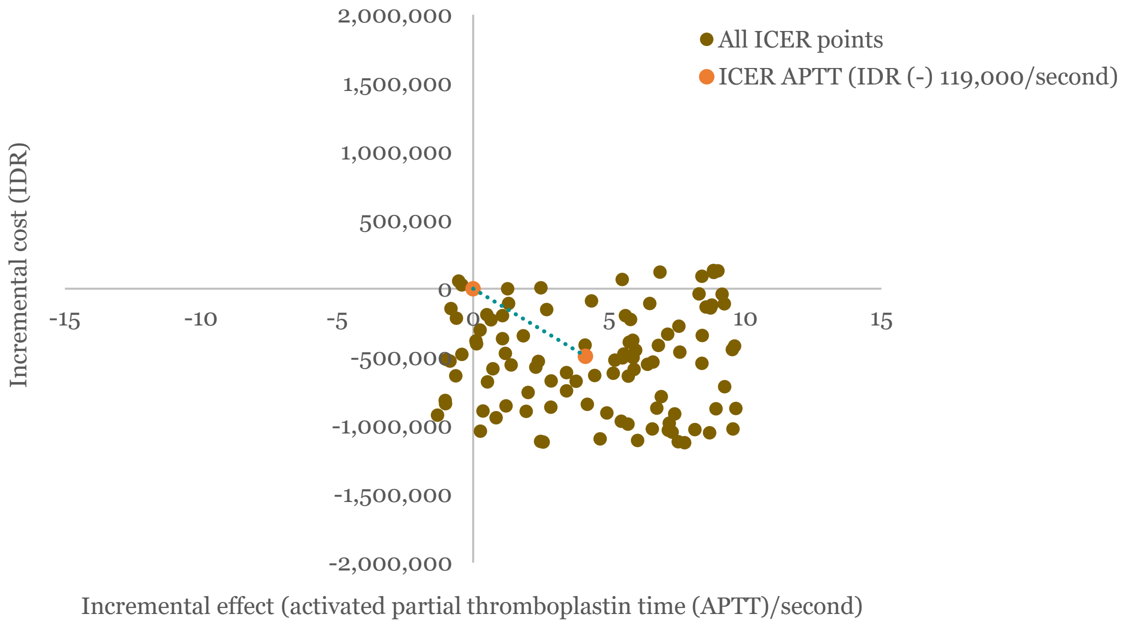

Figure 2. Cost-effectiveness plane of activated partial thromboplastin time (APTT).

Even though both ICER PT and APTT were in the same quadrant, there are still slight differences. The cloud formed from the ICER PT value was smaller, denser, and more centralized than the cloud obtained from the ICER APTT value. This was due to the large minimum-maximum range of the variables entered to get the ICER value. The standard deviation value of the input variable APTT was greater than the standard deviation value of the input variable PT.

Deterministic sensitivity analysis

Deterministic sensitivity analysis offers a robust method to assess the impact of varying key parameters on the incremental cost-effectiveness ratio between a combination of aspirin clopidogrel compared to a single aspirin. A tornado diagram provides insights into the stability and reliability of cost-effectiveness evaluations in healthcare decision-making. The results of the sensitivity analysis of PT can be seen in **Figure 3**. **Figure 4** depicts the sensitivity analysis of APTT.

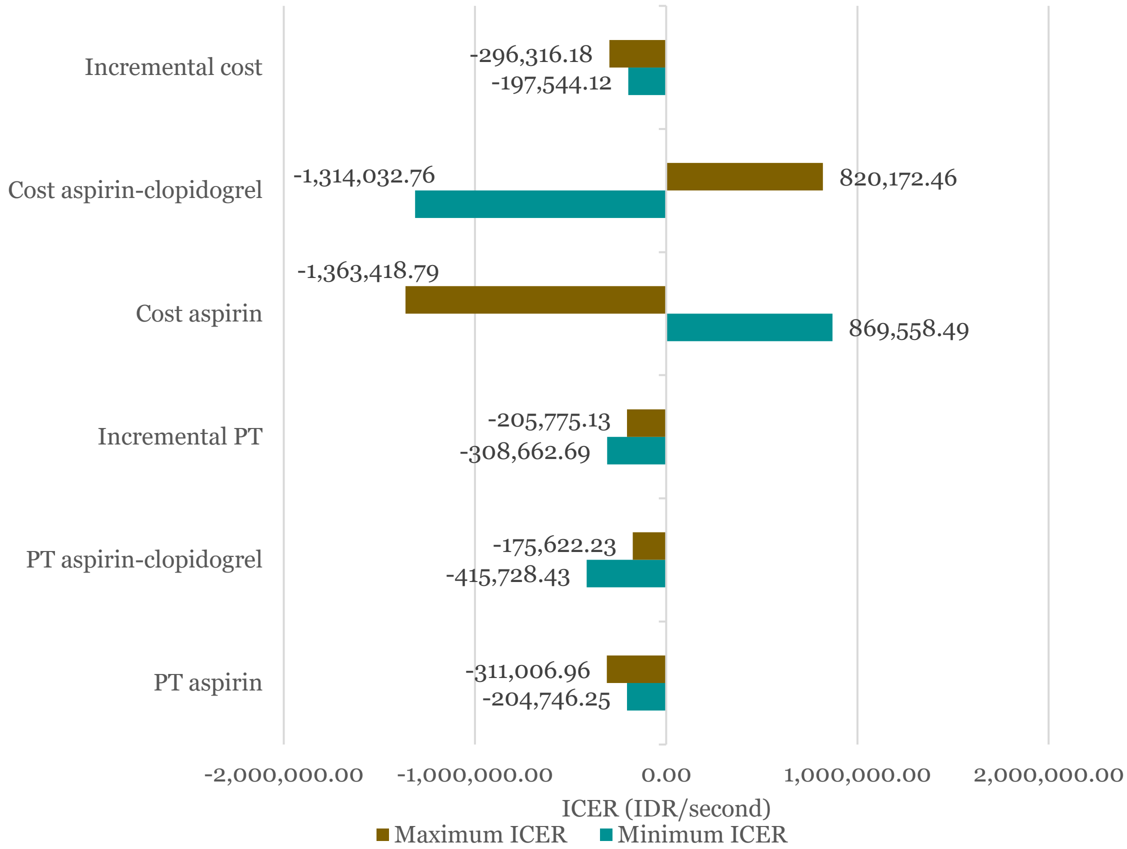

Figure 3. A tornado diagram of prothrombin time (PT) sensitivity analysis.

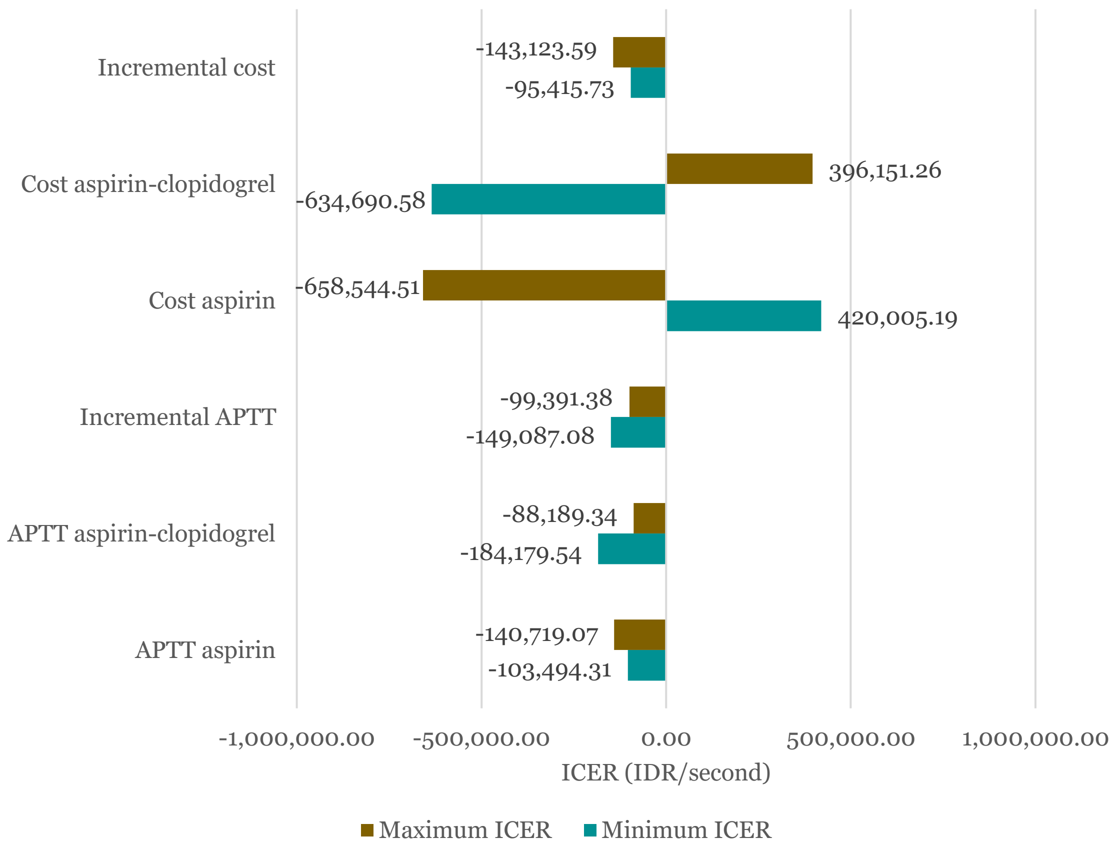

Figure 4. A tornado diagram of activated partial thromboplastin time (APTT) sensitivity analysis.

In the tornado diagram, it can be seen that the parameter that has a big influence on ICER was cost, both the cost of the combination of aspirin and clopidogrel and also direct medical costs. The green portion of the bar represents the ICER range when the parameter was lower than the actual ICER value, while the yellow bar represents the opposite. In **Figure 3** and **Figure 4**, it can be concluded that by reducing the cost of the aspirin-clopidogrel combination by 20%, the ICER value will be reduced to IDR -1,314,032 for a reduction in PT by one second, and IDR -634,690 for a decrease in APTT by one second.

Discussion

Research on sociodemographic differences related to various types of aspirin or combination therapies, such as aspirin-clopidogrel, typically involves extensive clinical trials or observational studies. However, the specific sociodemographic differences regarding these medications can vary based on the population studied and the specific study design [5,30-36]. It is important to note that while some studies might show differences in outcomes or responses among different demographic groups, these differences may not necessarily be solely attributed to the type of aspirin or combination therapy. Other factors, such as underlying health conditions, concurrent medications, lifestyle factors, or genetic variations, can also play significant roles [31,32].

The present study focused on evaluating the cost-effectiveness and clinical impact of aspirin-clopidogrel combination therapy compared to aspirin alone in managing ischemic stroke, addressing both clinical efficacy and economic feasibility. This study used rigorous inclusion and exclusion criteria to ensure relevance and accuracy. This study's analysis concentrated on crucial coagulation parameters (PT and APTT) and associated medical costs, using cost-effectiveness analysis (CEA) as a guiding framework. Our study also used sensitivity analysis via a tornado diagram to add robustness by assessing the impact of varying input parameters on the model's output.

Our data suggested the effectiveness value in the PT difference was longer aspirin-clopidogrel combination group than in the single aspirin group. The average effectiveness in the PT value difference for the single aspirin group was 2.05±2.96 while the value for administering the aspirin-clopidogrel combination was 4.04±5.50. This differs from the results obtained in 2020 study which found there was no significant difference between the combination or single groups in antiplatelet therapy on PT values [18].

In this study, not all patients experienced a decrease in APTT values, but some patients experienced an increase. Several factors influence differences in APTT value results, such as coagulation disorders, smoking, inflammation, hypertension, and other ischemic stroke risk factors that need to be taken into account because they can influence APTT values, resulting in an imbalance between the risk of bleeding and blood clotting control in ischemic stroke patients [37] . In line with Setyopranoto's research (2023), the results showed that the difference in APTT values between the administration of these two types of antiplatelet therapy, both single aspirin and clopidogrel combination, showed that there was no significant difference in APTT values in both the combination and single groups (p=0.09) or (p<0.05) [38].

Our data suggested the aspirin-clopidogrel combination group had higher cost-effectiveness than aspirin alone on PT parameters. The ICER value in aspirin-clopidogrel combination therapy was dominant over single aspirin with an ICER value of IDR (-) 474,315 for each second APTT decrease (**Figure 1**). This is in line with the study conducted by Lin *et al*. [4] which showed that administering clopidogrel and aspirin in the northeast quadrant for two years would result in a total of 8,776 and 8,576 quality-adjusted life years (QALYs) for ¥1,8777 ($2,838) and ¥12,302 ($1,859), respectively [4]. The ICER, which is the ratio of the difference in costs to the difference in QALYs, was calculated to be ¥32,382 ($4,893) per QALY gained [4]. Based on the ICER calculation, the ICER value for PT was at quadrant II suggesting that the health intervention has higher effectiveness with lower costs than standard intervention. Compared to the costs required for a single aspirin, the difference in clinical parameter values obtained is better and therefore it could be an option and consideration to be used [27,39].

Based on the results of the ICER calculation for the APTT value, it was found that the ICER was in quadrant II (IDR -119,270 (**Figure 2**)), meaning that the costs required for the aspirin-clopidogrel combination intervention were lower than the costs incurred for single aspirin, while the difference in clinical parameter values obtained better. Under these circumstances, it is clear that the proposed new intervention is superior [40].

However, this study has a limited sample size that might limit the generalizability of the findings, especially considering the complexity and heterogeneity of stroke patients. Utilizing retrospective data from medical records might introduce bias or missing information, affecting the accuracy of the analysis. Excluding patients with incomplete or unclear medical records and those who passed away during treatment might skew the results and limit a comprehensive understanding of real-world scenarios. In addion, this study was a single hospital which might limit the diversity of patient demographics and treatment variations, potentially impacting the external validity of the findings. The study only put disease complications that might not have considered all potential confounding variables that could influence the outcomes, such as comorbidities, medication adherence, or lifestyle factors, which could affect the cost-effectiveness outcomes.

Conclusion

The findings of this study underscore the potential benefits of employing the aspirin-clopidogrel combination in managing ischemic stroke, both from clinical and economic perspectives. By elucidating the cost-effectiveness of this combination therapy, our research demonstrates its superiority over aspirin alone in influencing crucial coagulation parameters, specifically PT and APTT. The ICER analysis revealed notable advantages of the aspirin-clopidogrel combination, showcasing its higher effectiveness with lower associated costs in managing PT and APTT values, essential markers influencing the clotting cascade in stroke patients. The placement of the combination therapy in the southeast quadrant of the ICER analysis signifies its dominance over the standard intervention (aspirin alone), indicating its potential as a more cost-effective alternative. These compelling results suggest that incorporating the aspirin-clopidogrel combination into routine stroke management protocols may offer enhanced clinical outcomes while being economically feasible. Consequently, our study emphasizes the considerable advantages this combination therapy presents, highlighting its potential to improve patient care and contribute positively to healthcare resource utilization in managing ischemic stroke.

Ethics approval

The protocol of the study was approved by Health Research Ethics Committee of Dr. M. Djamil Padan, Indonesia, with approval number LB.02.02/5.7/147/2023.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

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