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Evaluation of Antiplatelet Therapy Related to Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) Values in Relation to the Risk of Recurrent Stroke

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KEYWORDS
antiplatelet; aspirin; PT; APTT; recurrent stroke

ABSTRACT
Stroke is a medical emergency with significant mortality and morbidity, often influenced by platelet aggregation. Antiplatelet agents are crucial in stroke prevention, as they inhibit platelet function and reduce thrombus formation. Despite antiplatelet therapy, some patients experience recurrent strokes, necessitating further investigation into coagulation parameters like Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT). This study aims to explore the relationship between antiplatelet therapy and PT/APTT values in stroke patients to assess the risk of recurrent strokes. A comparative study was conducted on two groups of stroke patients: those using aspirin therapy and those not using it. PT and APTT measurements were taken at the start and end of a three-month observation period. Data were analyzed quantitatively, focusing on PT and APTT changes in each group. Results: PT values increased more significantly in the Non-Aspirin group (16.32%) compared to the Aspirin group (11.98%). APTT values also increased more in the Non-Aspirin group (4.97%) compared to the Aspirin group (4.73%). However, the statistical significance of the differences in PT and APTT between the groups was not observed ($p > 0.05$). The study concludes that there is no significant difference in PT and APTT values between patients using clopidogrel alone or in combination with aspirin, indicating no enhanced risk of recurrent strokes based on these parameters.

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INTRODUCTION

Stroke is a disease or functional brain disorder characterized by neurological deficits (neurological paralysis) resulting from the interruption of blood flow to the brain (Murphy & Werring, 2020). Simply put, an acute stroke is defined as a brain disease caused by the cessation of blood supply to the brain due to a blockage (ischemic stroke) or bleeding (hemorrhagic stroke). According to the World Health Organization (WHO) definition, stroke is a clinical manifestation of cerebral function disorders, either focal or global, that occur rapidly and last for more than 24 hours or result in death with no apparent cause other than a vascular disorder.

In 2020, 1 in 6 deaths from cardiovascular disease was due to stroke. Every 40 seconds, someone in the United States has a stroke, and every 3.5 minutes, someone dies from a stroke. Each year, more than 795,000 people in the United States experience a stroke, with about 610,000 being first-time or new stroke cases (Price, 2015). According to the 2018 Basic Health Research (Riskesdas), the prevalence of stroke in Indonesia increased from 7% to 10.9% over the past five years. Stroke is classified into two types: ischemic and hemorrhagic, often preceded by lesions or injuries to the arterial

blood vessels. Of all stroke occurrences, two-thirds are ischemic, and one-third are hemorrhagic. Ischemic stroke occurs due to a blockage of blood vessels by thromboembolism, resulting in ischemia in the area below the blockage. Risk factors for stroke are divided into modifiable and non-modifiable factors. Non-modifiable factors include age and gender, while modifiable factors include hypertension, diabetes mellitus, lipid profiles, alcohol consumption, and smoking (Glans et al., 2024). Stroke patients generally experience motor and cognitive function impairments. Motor function decline includes weakness or paralysis of the arms or legs or one side of the body, as well as difficulties in vision or hearing. Cognitive function decline in stroke patients includes difficulty thinking, difficulty speaking the correct words, and inability to recognize body parts (McKenna et al., 2017).

Platelet aggregation plays a crucial role in the pathogenesis of stroke, making drugs that interfere with platelet function essential in its treatment. Antiplatelet agents such as aspirin and clopidogrel are generally used for secondary stroke prevention in patients after an ischemic stroke or Transient Ischemic Attack (TIA). Antiplatelet drugs inhibit platelet aggregation, thereby preventing thrombus formation in blood vessels (Li et al., 2022). The function of platelet aggregation is literally 'critical'. Platelets aggregate intravascularly as arterial thrombi in response to bleeding into a gap or rupture in an atherosclerotic plaque pathologically, making platelet aggregation potentially lethal. In both physiological and pathological situations, the mechanism of aggregation is the same. Thus, separating the therapy from the harmful effects of antiplatelet drugs depends on exploiting the pathophysiological differences in the environment where aggregation occurs. In practice, the beneficial balance between the positive and negative effects of antiplatelet therapy is achieved by treating patients whose thrombotic risk clearly outweighs the risk of bleeding complications (Kearon et al., 2016).

Antiplatelets are a class of drugs that inhibit platelet aggregation so that they can cause inhibition of thrombus formation (McFadyen et al., 2018). There are different types of antiplatelets that can be used, such as cyclo-oxygenase-1 (COX-1) inhibitors (aspirin), P2Y12 receptor antagonists with ADP (thienopyridines such as ticlopidine, clopidogrel, prasugrel and ticagrelor), glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide and thyrofiban). Antiplatelet agents have significant benefits in stroke prevention, but they still carry the risk of bleeding, especially with dual antiplatelet use (Brown et al., 2021). Antiplatelet therapy is important for acute ischemic stroke. The administration of antiplatelet therapy can reduce the incidence of recurrent strokes from 68% to 24%. Additionally, high blood pressure (systolic > 140 mmHg, diastolic > 90 mmHg) can increase the risk of recurrent stroke (Chen et al., 2020).

The CHANCE (Clopidogrel in High-risk Patients with Acute Non-disabling Cerebrovascular Events) study showed that the combination of clopidogrel and aspirin was more effective in reducing the risk of recurrent stroke over 90 days compared to aspirin alone without increasing bleeding (Pan et al., 2019). The POINT (The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) study showed that the combination of clopidogrel and aspirin had a lower risk of ischemic stroke but a higher risk of bleeding over 90 days compared to aspirin alone.

Prothrombin time (PT) and activated partial thromboplastin time (APTT) are blood tests used to evaluate a patient's coagulation status (Tekle et al., 2022). PT is used to assess extrinsic coagulation factors, while APTT can detect the function of intrinsic coagulation factors and other coagulation components. These tests can help explain the causes of bleeding or blood clotting disorders. PT and APTT tests are often conducted clinically, especially in patients suspected of having coagulation disorders (Menegatti & Palla, 2020). In previous studies, the parameter used to evaluate the use of antiplatelet doses was the platelet aggregation value parameter. In patients receiving antiplatelet

therapy, such as aspirin or clopidogrel, PT and APTT do not always change significantly because these drugs work by inhibiting platelet aggregation rather than affecting the coagulation pathways measured by PT and APTT. However, understanding the patient's overall coagulation status remains important in managing stroke therapy, especially if there is a need for combination therapy with anticoagulants (Xian et al., 2016a).

The aim of this study is to understand the relationship between antiplatelet therapy and PT/APTT values concerning the risk of recurrent stroke.

This research benefits clinicians by providing valuable insights into optimizing stroke treatment strategies, particularly in adjusting antiplatelet therapy based on PT and APTT values to minimize recurrent stroke risks. Additionally, the findings could guide future clinical guidelines for balancing thrombotic and bleeding risks in stroke patients (Proietti et al., 2019).

METHOD

This research uses a quantitative research approach, where data collection is conducted through retrospective analysis of stroke patient records to obtain PT and APTT values and treatment outcomes. Data collection techniques include gathering patient medical records and laboratory test results, focusing on those receiving antiplatelet therapy. The data analysis techniques involve statistical analysis to compare PT/APTT values and stroke recurrence rates, using appropriate statistical tests to determine any significant associations between these factors.

Sample selection began with direct field orientation to patients visiting the outpatient clinic to determine the population receiving aspirin and non-aspirin antiplatelet therapy. Patients were informed about the study and signed an Informed Consent if they agreed to participate. Medical records were reviewed, and samples meeting inclusion and exclusion criteria were selected. Inclusion Criteria: Diagnosed stroke patients receiving outpatient treatment at RSUD Dungus Madiun, Patients receiving aspirin and non-aspirin therapy for at least two months, Patients who adhered to medication using the Morisky-8 questionnaire, indicating a score of 0, Patients willing to fill out the informed consent form. Exclusion Criteria: Patients not regularly attending follow-up appointments, deceased patients. Based on the 2013 Riskesdas prevalence of 13% coronary heart disease in East Java, a sample size of 20 patients was calculated, with 30 samples determined for representativeness.

Initial PT and APTT Test: The initial PT and APTT test was conducted one day after patients agreed to participate, with blood samples taken after fasting for 10-12 hours. Final PT and APTT Test: The final PT and APTT test was conducted three months after the initial test. Recurrent stroke observation was conducted three months after the study began, reviewing medical records for stroke recurrence and analyzing PT and APTT changes over three months. Data analysis involved processing research results, including patient characteristics such as age, gender, antiplatelet type, PT and APTT values, and recurrent stroke occurrence, presented descriptively in percentages (Mehari et al., 2023).

RESULT AND DISCUSSION

Selection of Research Samples

The process of selecting research samples conducted at the outpatient clinic of RSUD Dungus Madiun took place from April to May 2024. During the sample selection process, 380 patients with a diagnosis of stroke visited the outpatient clinic. Among these research samples, 207 patients received antiplatelet therapy with Aspirin, while 173 patients received Non-Aspirin antiplatelet therapy. From these two groups of potential research samples, the selection was made according to the inclusion and

exclusion criteria, resulting in 30 research samples for each group. The demographic data of the samples collected is presented in Table 1.

Table 1.
Demographic Data of the Samples

Patient Demographics	Number of Samples
Gender	
- Male	36
- Female	24
TOTAL	**60**
Age	
- Early Adulthood (22-44 years)	2
- Middle Adulthood (45-64 years)	53
- Elderly (≥ 65 years)	5
TOTAL	**60**
Type of Antiplatelet	
- Aspirin	30
- Non Aspirin	30
TOTAL	**60**

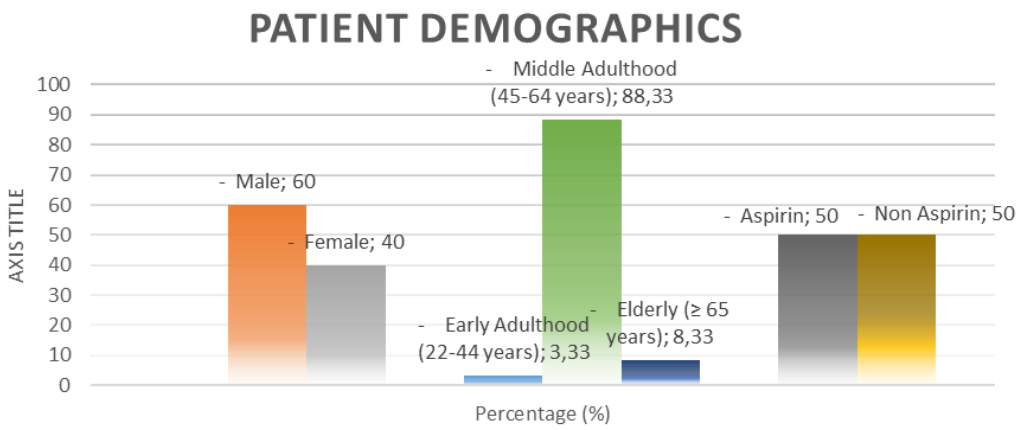

Figure 1. Percentage Patient Demographics

Based on the demographic data of the research samples, it is observed that the male sample has a higher percentage compared to females, accounting for 60%. Regarding age demographics, the majority of the research samples fall within the middle adulthood range (45-64 years), with a percentage of 88.33%

Initial PT and aPTT Value Assessment

The initial PT and aPTT values were assessed on samples that met the inclusion and exclusion criteria and agreed to sign the Informed Consent. Blood samples were collected from 30 individuals in the Aspirin group and 30 in the Non-Aspirin group at the laboratory of RSUD Dungus Madiun. Prior to blood collection, the participants were instructed to fast for 10-12 hours. The collected blood was placed in EDTA tubes and labelled with patient codes, followed by the assessment of the initial PT and aPTT values. The results of the initial PT and aPTT values are presented in Table 2.

Table 2.
Initial PT and aPTT Values

	Type of Antiplatelet	Initial PT Value (seconds)	Initial aPTT Value (seconds)	Sample	Type of Antiplatelet	Initial PT Value (seconds)	Initial aPTT Value (seconds)
1	Non-Aspirin	10,5	30,6	31	Non-Aspirin	9,7	30,2
2	Aspirin	9,3	31,9	32	Aspirin	8,9	28,5
3	Non-Aspirin	7,1	32,2	33	Aspirin	10,7	29,8
4	Aspirin	14,1	33,9	34	Non-Aspirin	11,5	30,1
5	Aspirin	15,6	32,4	35	Aspirin	10,8	28,7
6	Aspirin	14,5	32,9	36	Non-Aspirin	11,2	31,1
7	Non-Aspirin	14,1	31,8	37	Non-Aspirin	9,3	27,8
8	Non-Aspirin	11,7	30,8	38	Aspirin	13,1	30,1
9	Non-Aspirin	15,2	33,8	39	Non-Aspirin	10,7	31,7
10	Non-Aspirin	9,8	29,8	40	Aspirin	9,9	29,5
11	Aspirin	10,5	30,5	41	Non-Aspirin	12,3	31,2
12	Aspirin	9,8	28,7	42	Non-Aspirin	10,9	29,8
13	Non-Aspirin	11,2	31,2	43	Aspirin	11,8	29,5
14	Aspirin	14,1	30,8	44	Non-Aspirin	9,3	27,5
15	Non-Aspirin	9,3	29,9	45	Aspirin	12,2	30,1
16	Aspirin	11,8	29,9	46	Non-Aspirin	10,5	28,5
17	Aspirin	7,8	28,5	47	Aspirin	11,1	28,6
18	Non-Aspirin	10,8	30,8	48	Non-Aspirin	10,2	27,3
19	Aspirin	11,5	31,8	49	Aspirin	13,6	31,2
20	Aspirin	15,2	32,4	50	Aspirin	10,9	31,8
21	Non-Aspirin	10,4	27,5	51	Non-Aspirin	14,2	33,6
22	Non-Aspirin	10,2	29,6	52	Non-Aspirin	9,7	29,4
23	Aspirin	9,7	27,9	53	Aspirin	10,8	29,5
24	Non-Aspirin	10,8	29,5	54	Non-Aspirin	12,6	32,1
25	Aspirin	11,2	30,5	55	Aspirin	10,5	30,7
26	Aspirin	11,8	28,5	56	Non-Aspirin	13,4	31,6
27	Non-Aspirin	10,5	28,5	57	Aspirin	12,5	30,1
28	Aspirin	11,5	29,9	58	Non-Aspirin	9,8	28,4
29	Non-Aspirin	11,8	28,7	59	Aspirin	11,2	29,1
30	Non-Aspirin	8,5	29,5	60	Aspirin	14,3	35,2

Final PT and aPTT Value Assessment

The final PT and aPTT values were assessed three months after the initial assessment. Each sample from the Aspirin and Non-Aspirin groups was tested in the laboratory according to the agreed schedule. The process for collecting samples for the final PT and aPTT assessments was identical to that of the initial PT and aPTT assessments, with the blood samples placed in EDTA tubes and examined immediately. Before blood collection, each participant was instructed to fast for 10-12 hours. The results of the final PT and aPTT values are presented in Table 3.

Table 3.
Final PT and aPTT Value

Sample	Type of Antiplatelet	Final PT Value (seconds)	Final aPTT Value (seconds)	Sample	Type of Antiplatelet	Final PT Value (seconds)	Final aPTT Value (seconds)
1	Non-Aspirin	12,8	36,7	31	Non-Aspirin	11,2	300,8
2	Aspirin	12,7	31,4	32	Aspirin	11,5	30,6
3	Non-Aspirin	13,9	28,8	33	Aspirin	10,9	31,5
4	Aspirin	12,0	29,3	34	Non-Aspirin	12,7	31,5

Sample	Type of Antiplatelet	Final PT Value (seconds)	Final aPTT Value (seconds)	Sample	Type of Antiplatelet	Final PT Value (seconds)	Final aPTT Value (seconds)
5	Aspirin	16,2	35,2	35	Aspirin	11,5	30,5
6	Aspirin	15,7	36,3	36	Non-Aspirin	13,5	30,8
7	Non-Aspirin	16,3	34,5	37	Non-Aspirin	10,8	30,2
8	Non-Aspirin	13,2	33,3	38	Aspirin	12,8	31,3
9	Non-Aspirin	17,2	35,9	39	Non-Aspirin	11,5	30,8
10	Non-Aspirin	11,5	32,1	40	Aspirin	10,5	31,6
11	Aspirin	12,1	32,2	41	Non-Aspirin	13,8	33,4
12	Aspirin	11,5	30,5	42	Non-Aspirin	12,2	31,2
13	Non-Aspirin	12,2	30,8	43	Aspirin	12,5	31,3
14	Aspirin	15,7	31,5	44	Non-Aspirin	11,4	30,1
15	Non-Aspirin	10,9	31,5	45	Aspirin	14,0	31,6
16	Aspirin	13,8	31,8	46	Non-Aspirin	11,3	30,5
17	Aspirin	10,5	31,5	47	Aspirin	12,5	31,2
18	Non-Aspirin	12,6	29,5	48	Non-Aspirin	11,6	29,5
19	Aspirin	12,0	30,2	49	Aspirin	15,3	33,6
20	Aspirin	16,3	33,1	50	Aspirin	14,2	32,8
21	Non-Aspirin	11,5	30,5	51	Non-Aspirin	15,7	34,8
22	Non-Aspirin	11,4	30,6	52	Non-Aspirin	11,8	31,6
23	Aspirin	11,3	29,8	53	Aspirin	13,5	31,2
24	Non-Aspirin	12,2	31,2	54	Non-Aspirin	14,3	33,8
25	Aspirin	12,5	31,8	55	Aspirin	11,8	31,3
26	Aspirin	13,2	30,5	56	Non-Aspirin	14,2	33,8
27	Non-Aspirin	13,8	29,8	57	Aspirin	13,8	31,7
28	Aspirin	12,2	30,2	58	Non-Aspirin	11,4	30,1
29	Non-Aspirin	13,2	30,1	59	Aspirin	13,4	32,1
30	Non-Aspirin	10,8	31,2	60	Aspirin	16,8	38,4

Observation of Recurrent Stroke Incidents

The observation of recurrent stroke incidents was conducted three months after the samples participated in the study. The occurrence of recurrent strokes was evaluated based on the medical records of the samples, determining whether there was a history of hospital admission with a diagnosis of stroke. In addition to reviewing the history of recurrent stroke attacks, an analysis was conducted on the changes in PT and aPTT values during the three-month observation period, using data from the initial and final laboratory assessments of PT and aPTT values. Any changes, whether increases or decreases, could affect the condition of stroke patients using antiplatelets. This is because PT and aPTT assessments aim to evaluate the coagulation status of the patient, and these assessments are typically conducted in clinical settings, especially for patients suspected of having coagulation disorders (Hyatt & Brainard, 2016). Stroke therapy management places great emphasis on the patient's coagulation status to assess the likelihood of recurrent stroke incidents (Xian et al., 2016b). The results are presented in Table 4.

Table 4.
Recurrent Stroke Incident Data

Group	Recurrent Stroke	Total Samples
Aspirin	1	30
Non Aspirin	0	30

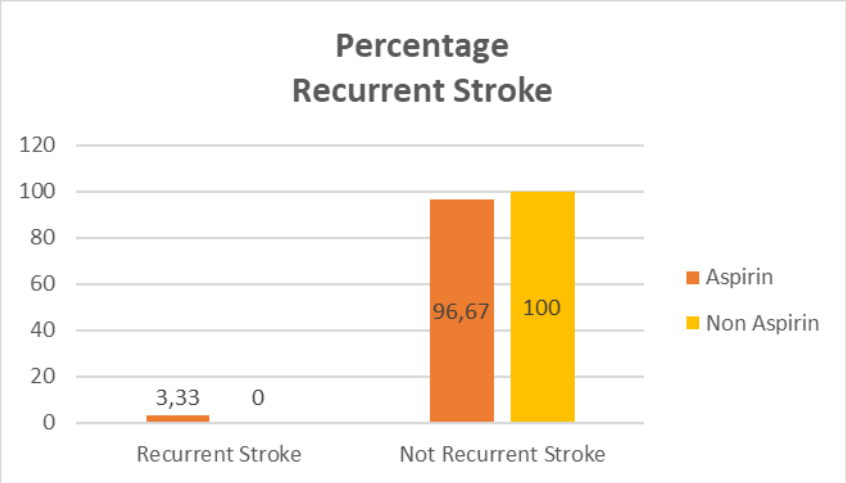

Figure 2. Percentage Recurrent Stroke

Based on the recurrent stroke incident data above, it was found that in the Aspirin group, there was 1 sample (3.33%) that experienced a recurrent stroke, while in the Non-Aspirin group, no samples experienced a recurrent stroke. A comparison of PT and aPTT values between the Aspirin and Non-Aspirin groups was conducted to determine the extent of the difference in PT and aPTT values in groups using Aspirin antiplatelet therapy versus those using Non-Aspirin antiplatelet therapy. The results of the comparison of initial and final PT and aPTT values between the two groups in Table 5. 6

Table 5.
Comparison of PT Values in Antiplatelet Therapy Use

Group	PT Value (Mean ± SD)		Description	Description
	Initial	Final		
Aspirin	11,69 ± 1,92	13,09 ± 1,78	⬆ 1,4 (11,98%)	11 – 18,9 detik
Non Aspirin	10,91 ± 1,74	12,69 ± 1,65	⬆ 1,78 (16,32%)	
p value	0,448	0,570		

Table 6.
.Comparison of aPTT Values in Antiplatelet Therapy Use

Group	PT Value (Mean ± SD)		Description	aPTT Normal
	Initial	Akhir		
Aspirin	30,43 ± 1,74	31,87 ± 1,91	⬆ 1,44 (4,73%)	25 - 48,45 detik
Non Aspirin	30,15 ± 1,71	31,65 ± 1,98	⬆ 1,5 (4,97%)	
p value	0,962	0,356		

Comparison between Aspirin and Non-Aspirin Groups in Terms of PT and aPTT Values Using the Independent t-test. The Independent t-test was used to calculate the comparison between the Aspirin and Non-Aspirin groups regarding PT and aPTT values. It was found that the PT value in the Non-Aspirin group showed a greater increase compared to the Aspirin group, with the Non-Aspirin group experiencing an increase of 16.32%, while the Aspirin group experienced an increase of 11.98% from

the initial average PT value. The significance value for both initial and final PT values between the Aspirin and Non-Aspirin groups had a p-value > 0.05.

From the comparison test results, the aPTT value data showed that the Non-Aspirin group had a greater increase in aPTT values compared to the Aspirin group, with the Non-Aspirin group experiencing an increase of 4.97%, while the Aspirin group had an increase of 4.73%. The significance value for the initial and final aPTT values in both the Aspirin and Non-Aspirin groups showed a p-value > 0.05. This is consistent with previous research, which stated that there is no significant difference (p = 0.803), meaning the use of Clopidogrel alone or in combination with Aspilet does not affect PT and aPTT values in stroke patients.

The selection of research samples conducted at the outpatient clinic of RSUD Dungus Madiun was carried out from April to May 2024. The research sample groups were categorized according to inclusion and exclusion criteria, resulting in 30 research samples for each group. Based on the demographic data obtained, it was found that the sample with male gender had a larger percentage compared to females, which was 60%. This is because males have a higher risk factor for experiencing a stroke. According to research, males have the hormone testosterone, which can increase LDL levels. High LDL levels will increase cholesterol levels, thereby increasing the risk of degenerative diseases such as ischemic stroke. Moreover, women are more protected from heart disease and stroke until middle age due to the estrogen hormone they possess. After menopause, women's risk is the same as men's for stroke and heart disease (Ryczkowska et al., 2023).

Another demographic data point is age. The age range that is most prevalent in the research sample is middle adulthood (45-64 years), which is 88.33%. This is because the older the age, the higher the risk of having a stroke. This is similar to research findings that state that with increasing age, the incidence of cerebral ischemia increases regardless of ethnicity and gender. After the age of 55, the incidence will double every decade (Ryczkowska et al., 2023).

The initial PT and aPTT values were measured on samples that met the inclusion and exclusion criteria and were willing to sign the Informed Consent. Before blood sampling, the samples were informed to fast for 10-12 hours. The final PT and aPTT values were measured after 3 months from the initial examination. Each sample was from the Aspirin and Non-Aspirin groups.

Recurrent Stroke Events were observed 3 months after the samples participated in the study. The occurrence of Recurrent Stroke was determined from the samples' medical records, indicating whether there was a history of hospital admission with a stroke diagnosis. In addition to reviewing the history of recurrent stroke events, an analysis of changes in PT and aPTT values over the 3-month observation period was also conducted based on laboratory data of initial and final PT and aPTT values. Changes, whether increases or decreases, can affect the condition of stroke patients using antiplatelet therapy (Sandercock et al., 2014). This is because PT and aPTT examinations aim to evaluate the coagulation status of patients, particularly those suspected of having coagulation disorders. Stroke therapy treatment pays close attention to the patient's coagulation status to assess the likelihood of recurrent stroke events (Geng et al., 2024).

Based on the data of recurrent stroke events, it was found that in the Aspirin group, there was 1 sample (3.33%). The sample that experienced recurrent stroke was 67 years old, which falls into the elderly range, thus having a higher risk of recurrent stroke. This is consistent with previous research stating that ischemic events will increase with age, leading to an increased risk of cardiovascular death, MI, and stroke. Furthermore, in older age, there is also an increased risk of bleeding, which poses a risk of coagulation factor disorders (Barg et al., 2024). This results in abnormal PT and aPTT values.

The comparison between the Aspirin and Non-Aspirin groups regarding PT and aPTT values was calculated using the Independent t-Test. It was found that the PT value in the Non-Aspirin group had a greater increase compared to the Aspirin group. The Non-Aspirin group experienced an increase of 16.32%, whereas the Aspirin group experienced an increase of 11.98% from the average initial PT value. The significance values for both the initial and final PT values between the Aspirin and Non-Aspirin groups had a p-value > 0.05.

The aPTT values obtained from the comparison test showed that the Non-Aspirin group had a greater increase in aPTT values compared to the Aspirin group. The Non-Aspirin group experienced an increase of 4.97%, whereas the Aspirin group had an increase of 4.73%. For the significance values of the initial and final aPTT examinations, a p-value > 0.05 was obtained for both the Aspirin and Non-Aspirin groups. This is consistent with previous research stating that there is no significant difference (p = 0.803), meaning that the use of Clopidogrel alone or in combination with Aspilet does not affect PT and aPTT values in ischemic stroke patients.

CONCLUSION

The results indicate that there is no significant difference in the impact of using Clopidogrel alone or in combination with Aspilet on PT and aPTT values in stroke patients (p = 0.803). This finding suggests that both treatment approaches have a similar effect on these coagulation parameters, contributing to the understanding of antiplatelet therapy in stroke management. Future research could further explore different patient populations or additional factors that may influence these outcomes.

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