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Original article

A 4-year cross-sectional study on the basic demography and Clopidogrel resistance profile

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Abstract. *Background and aim:* Stroke is a leading cause of death and disability worldwide. Clopidogrel is widely used to prevent recurrent strokes in acute ischemic stroke patients, but clopidogrel resistance remains a significant concern due to various factors. While extensive research has been conducted on this issue, data from East Java are limited, and many cases are overlooked by clinicians. This study aimed to address this gap. *Methods:* We conducted a cross-sectional study involving 108 stroke patients aged 30–80 years who were not using proton pump inhibitors (e.g., omeprazole, esomeprazole) and had been on clopidogrel therapy for at least seven days. Clopidogrel resistance was evaluated using the VerifyNow assay. *Results:* Out of 108 patients, 27 (25%) were classified as having a bleeding risk. In terms of clopidogrel sensitivity, 79 patients (73%) were sensitive, while 29 (27%) were resistant. Among resistant cases, 17 were male and 12 were female. Age significantly influenced bleeding risk ($p = 0.006$), but not clopidogrel sensitivity ($p = 0.135$). Gender had a significant impact on inhibition levels ($p = 0.009$), as well as on base score ($p = 0.009$) and PRU score ($p = 0.035$). *Conclusions:* A notable proportion of stroke patients in East Java exhibited clopidogrel resistance, with males showing higher resistance rates. Age was a significant factor for bleeding risk, while gender influenced inhibition levels and PRU scores. Further research is needed to explore the underlying reasons for the observed gender differences in clopidogrel resistance. (www.actabiomedica.it)

Key words: age, clopidogrel, gender, resistance, sensitivity

Introduction

Stroke affects more than 7 million individuals worldwide each year and remains one of the leading causes of death and disability among adults. Approximately 85% of stroke cases are ischemic strokes, with about 50% of these caused by atherosclerotic thrombotic occlusion in the cerebral arteries. Antiplatelet therapy, including the use of clopidogrel, is the primary treatment for acute non-cardioembolic stroke, transient ischemic attack (TIA), and intracranial atherosclerotic disease (1).

The mechanism of clopidogrel involves binding to the P2Y12 receptor on platelets, which is a component of the adenosine diphosphate (ADP) signaling pathway, and it functions as part of dual antiplatelet therapy in combination with aspirin. Clopidogrel resistance is associated with increased platelet aggregation and thrombus formation, potentially leading to treatment failure or insufficient prevention of recurrent events (2). Clopidogrel resistance can be influenced by various factors, such as increased COX-2 enzyme activity due to inflammation, infection, and atherosclerosis, which lead to enhanced platelet reactivity. Additionally, interactions with drugs such as statins (simvastatin, atorvastatin, fluvastatin) may impact its effectiveness. Inhibition, for example, by dihydropyridine-type calcium channel blockers (amlodipine), which compete

with isoenzymes involved in metabolism (CYP3A4), as well as substrates of CYP2C19 and competitive inhibition, such as by proton pump inhibitors (omeprazole and esomeprazole), can also contribute to resistance. Another significant factor is individual genetic variation (1). A meta-analysis conducted in Iran showed that approximately 20.5% of the population in the country exhibited clopidogrel resistance (3), while research in Indonesia reported a prevalence of 14.3% in two hospitals: Cipto Mangunkusumo National General Hospital and the University of Indonesia Hospital (4). Despite the widespread knowledge of clopidogrel resistance, it remains largely neglected in Indonesia, and there have been no reports of clopidogrel resistance in East Java to date. This study aims to provide a profile of clopidogrel resistance in East Java, using Premier Hospital as a representative institution for the region, with the goal of increasing clinician awareness.

Patients and Methods

This study utilizes a cross-sectional design conducted over a four-year period (2021-2024) at Premier Hospital in Surabaya, Indonesia. It includes all types of stroke patients aged 30-80 years who are not currently using proton pump inhibitors (such as omeprazole and esomeprazole). Eligible participants must have been receiving clopidogrel therapy for a minimum of seven days. Ethical approval for this research was obtained from the University of Surabaya Ethical Committee, under approval number: 602/KE/VI/2025. VerifyNow levels are measured using the P2Y12 Assay to identify clopidogrel resistance, with results reported in P2Y12 reaction units (PRU). Data from VerifyNow includes PRU, baseline, and inhibition values. "PRU" stands for P2Y12 Reaction Units, which measures platelet aggregation through the P2Y12 receptor. A higher PRU suggests increased platelet reactivity and potential resistance to the drug. "Base" refers to the initial measurement before medication, and "% inhibition" shows how effectively the medication reduces platelet aggregation. The VerifyNow results classify clopidogrel resistance into non-responsive (PRU > 208), responsive (PRU ≤ 208), and bleeding risk (PRU < 95). The VerifyNow protocol for testing in the VerifyNow P2Y12 assay begins by inserting the test device into the VerifyNow instrument. After the device is in place, a blood sample collection tube, which has been gently inverted several times, is placed into the test device. Blood samples are obtained concurrently with routine tests, eliminating the need for repeated needle insertions. The data obtained are analyzed using statistical methods, including descriptive analysis, chi-square test, Mann-Whitney test, one-sample binomial test, and Pearson correlation.

Results

Participant profile

This study includes a total of 108 participants, consisting of 75 males and 33 females. The male group has an average PRU of 137.32, a base score of 209.5, and an inhibition rate of 40.9, with 17 individuals categorized as clopidogrel resistant. In contrast, the female group exhibits a higher average PRU of 166, a base score of 229.6, and a lower inhibition rate of 25.8, with 12 individuals classified as clopidogrel resistant (Table 1).

Age analysis shows that the predominant age group is individuals over 70 years old, with 40 participants, followed by the 60–69-year age group, which comprises 37 individuals. Regarding bleeding risk, 27 out of 108 patients (25%) are classified as risk of bleeding. In terms of clopidogrel sensitivity, 79 out of 108 patients (73%) are sensitive, while 29 (26.9%) are classified as resistant (Table 1).

Comparison between variables

To investigate whether age and gender influence inhibition, PRU, base, clopidogrel sensitivity status, and bleeding risk, we conducted comparisons. The results showed that bleeding risk is significantly influenced by age ($p = 0.006$) (Figure 1 A), while clopidogrel sensitivity status is not influenced by age ($p = 0.135$) (Figure 1 B). Regarding inhibition, gender has a significant impact ($p = 0.009$) (Figure 1 C), and similar results were found for base score ($p = 0.009$) (Figure 1 D) and PRU score ($p = 0.035$) (Figure 1 E), both of which are influenced by gender. In 108

Table 1. Demographic and Risk Profile of Participants

Mean	**PRU**	**Base**	**Inhibition**	**Clopidogrel resistant (n)**	
Male	137,32	209,5	40,9	17	
Female	166	229,6	25,8	12	
Profile	N	%	Min	Max	Mean
Gender					
Male	75	69,4			
Female	33	30,6			
Age					
30 – 39 Years	1	0,93	35	35	35
40 – 49 Years	13	12	41	49	46
50 – 59 Years	17	15,7	51	59	55
60 – 69 Years	37	34,3	60	69	65,7
> 70 Years	40	37	70	86	75,6
Risk of bleeding	27	25			
Clopidogrel sensitivity status					
Sensitive	79	73			
Resistant	29	26,9			

participants, clopidogrel-sensitive participants had a significantly lower compared to clopidogrel-resistant participants ($p < 0.001$) (Figure 1 F).

Correlation between variables

To explore the correlation between variables, we conducted Pearson correlation analysis, which is presented as a heatmap in Figure 2. Significant correlations were found between age and PRU ($r = 0.318$; $p < 0.001$), age and inhibition ($r = 0.34$; $p < 0.001$), and age and bleeding risk ($r = 0.298$; $p = 0.002$). Additionally, gender was negatively correlated with base in females ($r = -0.201$; $p = 0.037$) and positively correlated with inhibition ($r = 0.34$; $p < 0.001$). Other correlations, including those between PRU, base, inhibition, bleeding risk, and clopidogrel sensitivity, were not explored further, as they have already been established.

Discussion

The resistance to clopidogrel is known to be associated with an increased risk of recurrent stroke and suboptimal neurological recovery (5). Despite this well-established understanding, the issue remains largely underrecognized by clinicians in Indonesia. A previous study reported the prevalence of clopidogrel resistance in Indonesia. Specifically, the study conducted in Jakarta observed a resistance rate of 14.3% (4). In our study, we found a higher clopidogrel resistance in male participants compared to females. This finding contrasts with a study conducted in China, which reported a clopidogrel resistance rate of 41.7%, with a predominance in females (7). The observed disparity could potentially be explained by hormonal differences. In females, higher estradiol levels promote the release of prostacyclin, which inhibits platelet aggregation, while progesterone suppresses inflammation. These factors may make females more prone to clopidogrel resistance. However, several factors, including body mass index (BMI), inflammation, and single nucleotide polymorphisms (SNPs), were not examined in our study (8). This represents a limitation that may help explain the higher prevalence of clopidogrel resistance observed in males in our study. Despite the observed gender differences, our findings are consistent with previous studies reporting higher PRU values in females compared to males (9). In

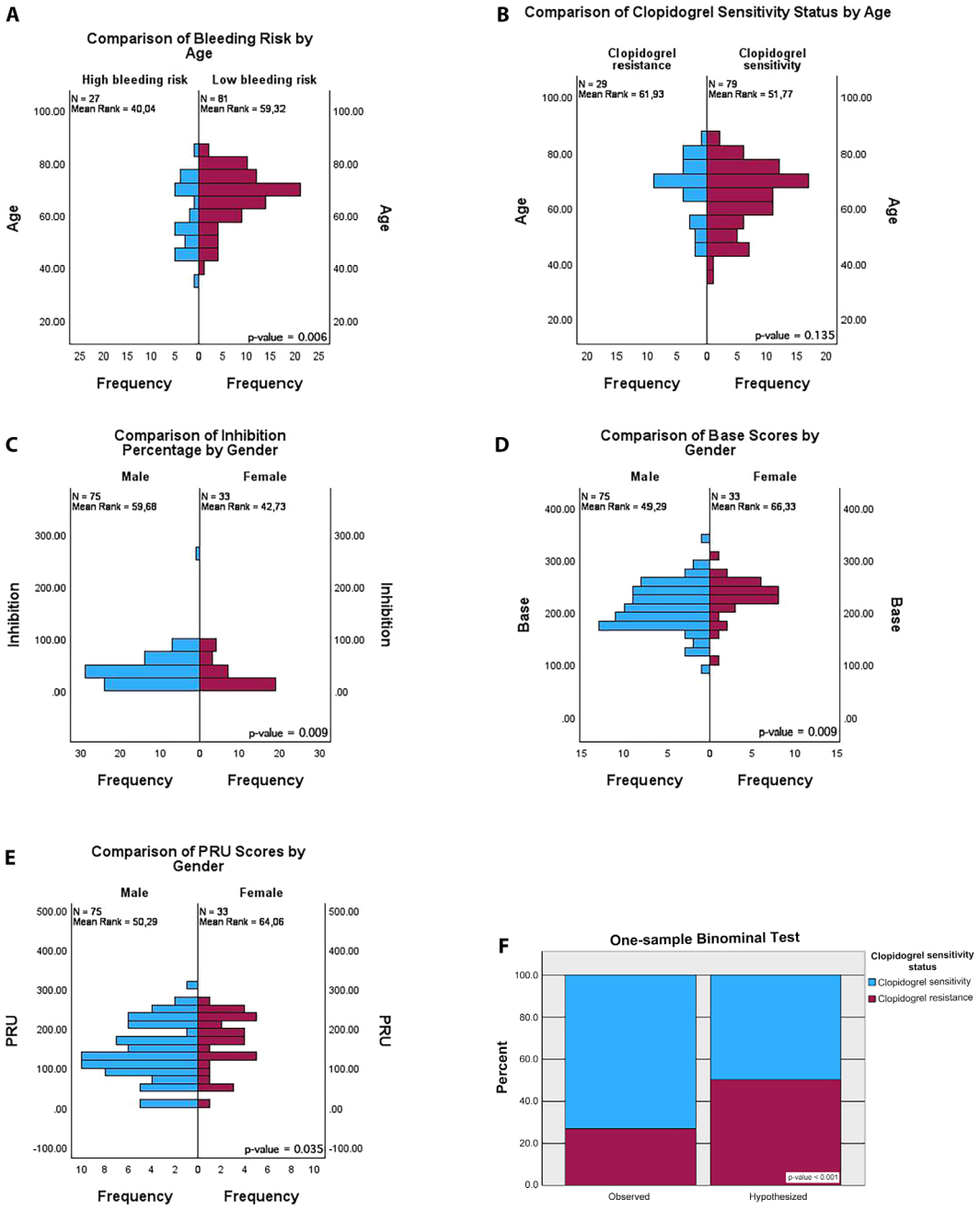

Figure 1. Statistical Comparison of Age, PRU, Base, and Inhibition by Gender, Bleeding Risk. (A) Bleeding Risk vs. Age. (B) Clopidogrel Sensitivity Status vs. Age. (C) Inhibition vs. Gender. (D) Base Score vs. Gender. (E) PRU Score vs. Gender. (F) Comparison of Clopidogrel Sensitive and Resistant.

our study, age was significance difference and positively correlated with PRU, inhibition, and bleeding risk. This could be attributed to the reduced metabolism of clopidogrel in older adults, as clopidogrel is a prodrug that requires metabolic activation. Aging leads to a 10.7% decrease in clopidogrel metabolism, as demonstrated in in vitro studies, likely due to the age-related decline in CYP450 enzyme activity (10). According to the risk of bleeding, 25% of our participants are at risk of bleeding. This finding is similar to a previous study, which found

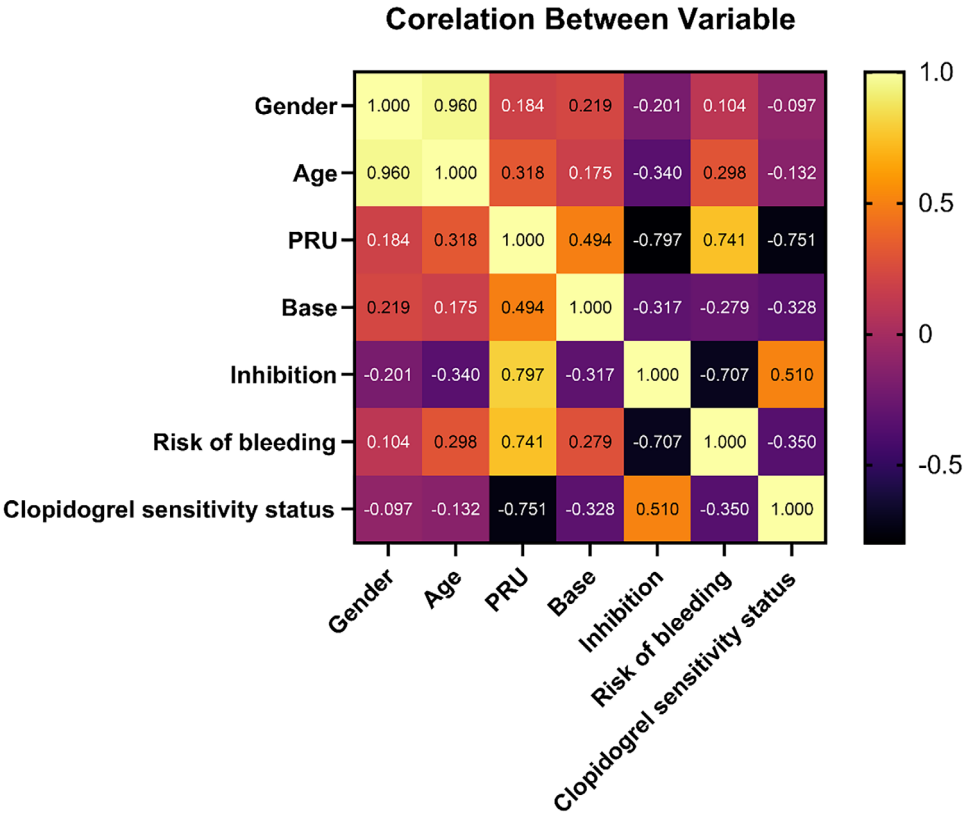

Figure 2. Heatmap of the Correlation for Gender, Age, PRU, Base, Inhibition, Bleeding Risk, and Clopidogrel Sensitivity Test.

that 24.6% of 57 Indonesian participants had a bleeding risk (9). The bleeding risk is associated with hyperresponsiveness to clopidogrel therapy. However, it is important to emphasize that this represents a risk and does not guarantee the occurrence of bleeding. This information is crucial for predicting potential ischemic or hemorrhagic complications. In patients who hyper-respond to clopidogrel, their dosing regimen may be adjusted to every other day instead of daily (1). Clopidogrel resistance should be clinically suspected, especially in cases of recurrent stroke despite the use of antiplatelet therapy or other related conditions. Addressing clopidogrel resistance requires assessing whether it arises from pharmacokinetic or pharmacodynamic factors.Alternative strategies include adjusting the clopidogrel dosage or switching to another P2Y12 inhibitor. However, confirming clopidogrel resistance is strongly recommended, regardless of whether clinical manifestations are absent or fully developed. When considering a switch to another P2Y12 inhibitor, it is essential to distinguish between prodrug P2Y12 inhibitors (e.g., clopidogrel, prasugrel) and active P2Y12 inhibitors (e.g., ticagrelor). Prodrugs like clopidogrel and prasugrel undergo distinct metabolic processes: clopidogrel is primarily metabolized by CYP2C19 and CYP3A4, while prasugrel is primarily metabolized by CYP3A4 and CYP2B6 (11). Regarding screening, including the analysis of SNPs, such testing is recommended but not mandatory, as SNP frequencies are ethnicity-dependent and may not be universally applicable (12). However, when a country has established SNPs associated with clopidogrel resistance, their use for clinical decision-making is considered acceptable.

Limitation

This study does not account for potential confounding factors that may influence clopidogrel

resistance, including BMI, blood pressure, renal status, diabetes, infection, inflammation, atherosclerosis, platelet turnover conditions (such as myocardial infarction and coronary artery bypass graft), or genetic polymorphisms. Additionally, the absence of a longitudinal design limits the ability to provide a more comprehensive understanding of these factors over time.

Conclusion

Clopidogrel resistance poses a significant challenge for clinicians, as it is associated with an elevated risk of recurrent strokes and poor neurological recovery, yet it remains underrecognized in clinical practice in Indonesia. This descriptive study does not address causality. Future research should investigate gender-based differences in drug response and delve deeper into factors such as BMI, SNPs, and inflammation to improve understanding and optimize therapeutic strategies for patients undergoing antiplatelet therapy.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: VB, FMH, BN Conceptualized the idea for the article, conducted the literature search, and performed the data analysis; FMH Drafted the manuscript; VB, BN Critically revised the work and editing.

Declaration on the Use of AI: None.

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