

Role of platelet count, platelet indices, and immature platelet fraction as potential markers for monitoring platelet reactivity in patients with acute coronary syndrome undergoing percutaneous coronary intervention



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ABSTRACT

The acute coronary syndrome is an acute manifestation of coronary heart disease, which is caused by a ruptured plaque of the coronary artery, thus forming a thrombus formation and resulting in myocardial infarction. Reperfusion therapy in patients with acute coronary syndrome is needed with the aim of preventing the area myocardium from experiencing necrosis by percutaneous coronary intervention using a stent, but this action may be caused by stent re-stenosis, bleeding, or thrombosis. Treatment with dual antiplatelet therapy in patients with acute coronary syndrome after percutaneous coronary intervention is recommended for used to prevent stent restenosis events or bleeding. A combination of aspirin and P2Y12 inhibitors is commonly used, such as thienopyridine-like clopidogrel and prasugrel as well as non-thienopyridine class drugs to reduce the thrombosis formation. Monitoring DAPT after PCI requires monitoring the reactivity platelet by platelet aggregation test, but this examination is rarely carried out because it needs special tools and a fairly expensive inductor. Another marker that is less noticeable is the platelet marker by complete blood count (CBC), which uses a hematology analyzer such as platelet count, which decreases and indicates bleeding. Index platelets (PDW, P-LCR, MPV, and PCT) reflect that platelet reactivity indicators and immature platelet fraction shows the proportion of thrombopoiesis. This review provides a summary of ACS (Definition, classification, and pathophysiology), PCI (Definition, clinical indication, characteristics of stent and complication of PCI), Combination of dual antiplatelet therapy and Platelet measure for monitoring ACS after PCI (Platelet count, index platelets like PDW, P-LCR, MPV, PCT and immature platelet fraction).

Keywords: Platelet count, platelet distribution width, platelet-large cell ratio, mean platelet volume, platelet crit, immature platelet fraction, percutaneous coronary intervention, acute coronary syndrome.

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INTRODUCTION

Acute coronary syndrome (ACS) encompasses acute manifestations of coronary heart disease resulting from the rupture of atheroma plaque within coronary blood vessels, contributing significantly to global mortality, affecting approximately 17.9 million individuals worldwide, with 85% of cases attributed to acute coronary syndrome.^{1,2} The rupture or erosion of atheroma plaque initiates platelet aggregation and activates the coagulation pathway, culminating in thrombus formation that can partially or totally obstruct the lumen of coronary vessels, leading to the classification of the syndrome into ST-elevation myocardial

infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UAP).^{3,4} Patients with STEMI require immediate reperfusion interventions to prevent the expansion of myocardial ischemia and necrosis, typically achieved through percutaneous coronary intervention (PCI).⁵

PCI involves coronary revascularization with the goal of dilating narrowed blood vessels through stenting.⁶ However, stenting during the procedure may induce micro-injuries around the stent, posing a risk of thrombosis.⁷ Managing stent thrombosis complications is crucial, and prevention involves reducing risk factors

through dual antiplatelet therapy (DAPT) to mitigate the risk of major adverse cardiovascular events (MACEs) and cardiovascular-related mortality.⁸

The recommended DAPT regimen combines aspirin with P2Y12 platelet inhibitors such as clopidogrel, prasugrel, and ticagrelor.⁹ While DAPT therapy post-PCI is effective in reducing thrombosis, it also elevates the risk of bleeding complications.¹⁰ Monitoring for excessive platelet reactivity is necessary due to the potential risk of bleeding and platelet stents resulting from DAPT following PCI.¹¹

Traditionally, monitoring platelet reactivity post-PCI involves the platelet

aggregation test (TAT).¹² However, TAT has limitations, including its infrequent application in laboratories due to the specialized equipment and relatively high costs associated with the procedure.¹³ An alternative, cost-effective method, often underutilized for monitoring platelet reactivity after PCI, involves assessing platelet count, platelet indices, and immature platelet fraction using a hematology analyzer. This approach aims to prevent thrombosis and bleeding events through routine monitoring of complete blood hematology examinations.¹⁴ This literature review aimed to explain how the platelet count, indices platelet and immature platelet fraction can be used to monitor platelet reactivity against the platelet aggregation test in acute coronary syndrome with percutaneous coronary intervention.

Acute Coronary Syndrome

Definition and Classification of Acute Coronary Syndrome

Acute coronary syndrome (ACS) denotes the condition of myocardial ischemia resulting from plaque rupture or atherosclerosis, accompanied by changes in plaque composition and thinning of the fibrous layer covering the plaque.¹⁵ Subsequently, this process triggers platelet aggregation and activation of the coagulation pathway, leading to thrombus formation, causing either total or partial occlusion of the coronary vessel.^{16,17} Total occlusion of coronary vessels resulting from ACS does not consistently lead to myocardial infarction with STEMI, whereas partial occlusion results in myocardial infarction, specifically NSTEMI and UAP.^{2,18} The differentiation between NSTEMI and UAP lies in the examination of cardiac markers, particularly troponin. A significant increase in cardiac markers occurs in myocardial infarction with NSTEMI.¹⁹

Pathophysiology of Acute Coronary Syndrome

Atherosclerosis stands as the primary cause of ACS and represents a chronic inflammatory process characterized by lipid accumulation in the coronary artery wall, resulting in thickened intima.²⁰ Endothelial dysfunction serves as a

pivotal abnormality initiating the earliest stages of atherogenesis, leading to an imbalance between vasoconstriction and vasodilation.²¹ Platelets assume a critical role in the formation of atherosclerotic plaques, particularly in thrombus formation, until plaque rupture occurs. Impaired Nitric Oxide (NO) production in the endothelium, triggered by ox-LDL, induces platelets to become hyperactive through Src and Rho kinase pathways, releasing chemokines that support atherosclerosis development, endothelial dysfunction, and foam cell formation.²² Activated platelets release various mediators, fostering adhesion, coagulation, and proteolysis while synthesizing chemokines and proinflammatory cytokines that expedite plaque formation.¹⁶ The process of atherosclerotic plaque formation initiates lesions that progressively obstruct blood flow, culminating in ischemia and, eventually, thrombosis. Physical disruption of the atheroma plaque predisposes it to thrombus formation.²¹ The fibrous cap may thin, tear, and release the lipid core into the bloodstream, activating coagulation factors. Activation of the coagulation cascade, involving both intrinsic and extrinsic pathways, subsequently triggers thrombin, converting fibrinogen into fibrin monomers, forming a platelet-rich thrombus and a solid clot.²³

This thrombus, in turn, obstructs the lumen of the coronary vessels, either partially or entirely.¹⁷ The resulting diminished blood flow due to this occlusion induces myocardial ischemia, which, if oxygen is halted for approximately 20 minutes, leads to myocardial necrosis (myocardial infarction).²⁴

Definition of PCI (Percutaneous Coronary Intervention)

Percutaneous coronary intervention (PCI), also known as coronary angioplasty, is a revascularization procedure conducted to address obstructive coronary artery disease, encompassing conditions such as unstable angina and acute myocardial infarction. This procedure is carried out by clinicians in a catheterization room, aiming to dilate narrowed blood vessels using stents.^{25,26}

The clinical indications for employing

percutaneous coronary intervention include STEMI, NSTEMI, and UAP.²⁶ PCI is a revascularization procedure conducted by clinicians with the goal of dilating narrowed blood vessels using stents.⁶ Stenosed coronary arteries can be addressed with either drug-eluting stents (DES) or bare metal stents (BMS).²⁷

Drug-eluting stents are designed to release drugs with the purpose of preventing fibroblast proliferation around the stent, thus averting in-stent restenosis.²⁷ These drugs inhibit the epithelialization of healing micro-lesions caused by ring deployment, which could otherwise lead to wound exposure in blood vessels and trigger thrombosis. Under these circumstances, DAPT is necessary to support reperfusion with PCI. The recommended DAPT duration for BMS stents is at least one month post-implementation, while for DES stents, it is extended to six months after implantation.²⁸

The primary factors influencing stent selection encompass various considerations: a) technical and clinical factors associated with an elevated risk of restenosis, including conditions such as diabetes mellitus, long or complex stenosis, acute myocardial infarction, in-stent restenosis of a BMS, and total coronary artery occlusion; b) Patient factors, such as the patient's ability to adhere to treatment, particularly concerning the administration of a shorter dual antiplatelet therapy.¹⁰

Intraprocedural Stent Thrombosis

While stenting coronary arteries during Percutaneous Transluminal Coronary Angioplasty (PTCA) has shown substantial clinical improvement, it remains associated with stent thrombosis, contributing to elevated morbidity and mortality rates.¹⁰

Stent thrombosis is linked to acute ischemia, infarction, hemodynamic instability, and death. Intraprocedural stent thrombosis (IPST) refers to the formation of a new thrombus, leading to occlusion or occurring shortly after stent implantation but before the completion of the PTCA procedure. Stent thrombosis is particularly associated with STEMI and sudden cardiac death. Lesions experiencing stent thrombosis are more

prone to developing an aneurysm, large thrombus, and exhibiting significant residual stenosis.¹⁰

Categories of stent thrombosis are classified as follows: a) probable - Unexplained death occurring within 30 days of the procedure or myocardial infarction at any time before the initiation of PCI; b) possible - Unexplained death occurring within 30 days after the PCI procedure.¹⁰

The timing of stent thrombosis can be categorized into four groups, such as acute stent thrombosis (0-24 hours after stent implantation), subacute stent thrombosis (24 hours-30 days after stent implantation), late stent thrombosis (30 days-1 year post stent implantation), very late stent thrombosis (> 1 year).¹⁰

The incidence of stent thrombosis typically occurs after the patient leaves the cardiac catheterization laboratory rather than intra-procedurally. Intraprocedural stent thrombosis refers to the formation of a new thrombus or an increase in thrombus compared to its baseline, leading to occlusion or occurring at some time after stent implantation but before the completion of the PTCA procedure.¹⁰

Risk factors contributing to an increased occurrence of stent thrombosis can be categorized into patient characteristics (including gene polymorphisms, inadequate antiplatelet use, and resistance to the antiplatelet effects of acetylsalicylic acid (ASA) and thienopyridine groups), lesion characteristics (including the presence of bifurcation lesions, long lesions, small vessel diameter, total chronic occlusion, diffuse disease, and lesions with thrombus formation), and procedural characteristics (including incomplete stent expansion, stent malpositioning, placement of stents in small vessels or using small stent diameters, multiple stent placements, particularly those over existing thrombus or stents with residual dissection or previous thrombus).¹⁰

The primary emphasis in managing stent thrombosis lies in prevention by addressing these risk factors and optimizing procedures. A key intervention is the early initiation of DAPT, especially for patients with acute coronary syndrome. Additionally, it is essential to screen patients for compliance with DAPT

use, assess bleeding risks, and carefully plan surgeries within the first 12 months following PTCA.¹⁰

DAPT in Patients Undergoing PCI

Antiplatelets play a crucial role in modifying platelet adhesion, activation, and aggregation in the thrombosis process during the treatment of ACS, particularly following the percutaneous coronary intervention, aiming to prevent stent thrombosis (in-stent restenosis), recurrent myocardial ischemia events, and major adverse cardiovascular events (MACEs).⁸

Aspirin, or acetylsalicylic acid (ASA), is an antiplatelet agent that operates by inhibiting the biosynthesis of thromboxane A₂, a crucial mediator in platelet activation, through the inhibition of platelet cyclooxygenase-1.⁸ The use of a single aspirin is deemed insufficient as it is considered ineffective in preventing vascular disease incidents in patients with symptomatic atherothrombosis. Recurrent vascular events in patients with ACS, despite single aspirin antiplatelet therapy, are attributed to either aspirin resistance or the inhibition of platelet activation through alternative pathways, specifically the P2Y₁₂ ADP receptor antagonists.⁸

Adenosine Diphosphate (ADP)-induced platelet aggregation plays a pivotal role in the arterial thrombosis process. P2Y₁₂ receptors are instrumental in inducing platelet activation and aggregation by ADP, making them crucial targets for inhibiting platelet aggregation. Clinically, widely used P2Y₁₂ antagonists include clopidogrel, ticagrelor, and prasugrel.⁸

Clopidogrel, a second-generation thienopyridine antiplatelet drug, undergoes oxidation by cytochrome P-450 in the liver and intestines. Its mechanism involves irreversible binding to the P2Y₁₂ receptor, inhibiting ADP-induced platelet aggregation.²⁹ Although the use of clopidogrel may lead to bleeding and stomach disorders, these side effects are generally less pronounced than those associated with aspirin. Clopidogrel metabolism takes place in the liver via cytochrome CYP3A4/3A5 and involves a two-stage process to form active metabolites. This metabolic pathway poses potential drug interactions, increasing

the risk of therapeutic failure and thrombosis. The combination of aspirin with clopidogrel in dual antiplatelet therapy remains widely employed due to its effective antiplatelet aggregation effects with minimal bleeding side.^{29,30}

Prasugrel, a third-generation thienopyridine antiplatelet, undergoes conversion into active metabolites before binding to the P2Y₁₂ platelet receptor.¹¹ The active metabolite of prasugrel is considered more effective than clopidogrel, exhibiting a faster onset and inhibition, with consistent clinical responses in patients with ACS who undergo PCI. Prasugrel has demonstrated efficacy in reducing the incidence of Major Adverse Cardiovascular Events (MACEs).³¹ In patients with ACS, especially those having acute myocardial infarction with STEMI undergoing PCI, prasugrel is recognized as the most effective treatment of choice.¹¹ Dual antiplatelet therapy combining aspirin with prasugrel has been shown to significantly reduce ischemic events, although it is associated with a heightened risk of bleeding.³²

Ticagrelor belongs to the non-thienopyridine antiplatelet class of cyclopentyl triazolopyrimidines, operating by binding to the P2Y₁₂ receptor at a distinct site compared to the thienopyridine class. This binding renders the receptor inactive, inhibiting ADP activation, a key factor in platelet aggregation. Notably, ticagrelor does not require metabolism into active metabolites, and its inhibitory effect on platelet aggregation is reversible.³³ Ticagrelor is utilized as an antiplatelet therapy option, often in conjunction with aspirin, for patients having ACS with NSTEMI. The safety profile of ticagrelor is associated with a bleeding risk that, while not significantly different from clopidogrel, still presents a potential for bleeding events.³⁴

The utilization of dual antiplatelet therapy following PCI in patients with ACS is acknowledged for its potential to reduce thrombosis incidence. However, it also comes with an increased risk of bleeding complications. Stent thrombosis may still manifest in up to 0.5-2% of elective PCI cases and > 6% of PCI cases involving ACS, despite the administration of dual

antiplatelet agents.¹⁰ It is crucial to monitor the risk of bleeding and the incidence of stent thrombosis after PCI with dual antiplatelet therapy, aiming to assess platelet reactivity and identify recurrent ischemic events.¹¹ Platelet reactivity after PCI is typically monitored using the light transmission method in TAT.^{12,35} However, this method has limitations, including its infrequent application in laboratories due to the specialized equipment and relatively high costs associated with the procedure.¹³

Platelet Count in ACS Patients Undergoing PCI

An alternative and cost-effective method often underutilized in monitoring platelet reactivity after PCI is the assessment of platelet count, platelet indices, and immature platelet fraction parameters using a hematology analyzer (HA).¹⁴ Platelet count is a routine and widespread examination that determines the number of platelets present in 1 µl of blood. Under normal circumstances, platelets tend to aggregate and become adhesive during the coagulation process. A decrease in platelet count by < 50% can indicate a tendency toward bleeding, while conversely, in instances of excessive clotting, the platelet count in the blood may be elevated.³⁶

Platelet Indices in ACS Patients Undergoing PCI

The platelet indices encompass platelet distribution width (PDW), mean platelet volume (MPV), platelet-large cell ratio (P-LCR), and platelet criterion (PCT). PDW serves as a measure of the diameter of platelets in peripheral blood. Elevated PDW levels indicate a larger and more active platelet fraction, making PDW a proposed more specific indicator of platelet reactivity compared to MPV.³⁷ Mean Platelet Volume (MPV) represents the average size of platelets circulating in peripheral blood.³⁸ In ACS patients, an increased MPV value can serve as an indicator of larger and more reactive platelet size, being associated with myocardial infarction and predicting an unfavorable outcome of PCI.³⁷

P-LCR is the proportion of normal platelets that are > 12 fL and serves as a valuable marker to assess megakaryocyte activity. An elevated P-LCR indicates

excessive megakaryocyte activity.³⁹ PCT reflects the total platelet mass and is associated with the prognosis in acute vascular conditions. An elevated PCT is considered one of the independent predictors of long-term cardiovascular mortality.⁴⁰

Immature Platelet Fraction in ACS Patients Undergoing PCI

Immature Platelet Fraction (IPF) serves as a pertinent laboratory parameter utilized to gauge platelet activity, with its measurement correlating with the count of young platelets containing RNA molecules. IPF reflects the proportion of immature platelets in comparison to the total platelet count. In ACS patients, an elevated IPF value is indicative of an increase in thrombopoiesis and platelet turnover. The assessment of thrombopoiesis activity through IPF examination can be effectively conducted as part of a complete blood count (CBC) using the flow cytometry method.⁴⁰

CONCLUSION

In conclusion, the management of ACS with myocardial infarction necessitates immediate reperfusion through PCI to avert the expansion of the necrotized myocardial area. However, this intervention poses risks such as micro-injuries due to stent opening (in-stent restenosis) or thrombosis, prompting the requirement for DAPT combining aspirin with ticagrelor, prasugrel, or clopidogrel. Nevertheless, the implementation of PCI alongside DAPT introduces a risk of bleeding, necessitating vigilant monitoring measures to assess platelet reactivity and prevent recurrent ischemic events through routine CBC marker tests on platelet count examinations. In ACS patients after undergoing PCI with dual antiplatelet therapy, platelet count examinations revealing thrombocytopenia suggest bleeding tendencies. During the assessment of platelet indices, an elevated PDW indicates a large and active platelet fraction. An increased P-LCR indicates heightened megakaryocyte activity. An increased MPV indicates larger and more reactive platelets. An increased PCT indicates long-term cardiovascular mortality prediction, while an increased

IPF indicates platelet turnover and heightened thrombopoiesis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHOR CONTRIBUTION

The manuscript was written, reviewed, and revised by INA and YH. All authors actively contributed to the development of the manuscript and have given their approval for the final version.

ETHICAL CLEARANCE

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