

Relationship of platelet indices with acute stent thrombosis in patients with acute coronary syndrome

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Abstract

Introduction: Despite major advances in stent technology and antithrombotic therapy, the development of stent thrombosis continues to be a major problem in patients who have undergone percutaneous coronary intervention (PCI). Although a few studies have investigated the relationship between early stent thrombosis and platelet activity, the relationship between acute stent thrombosis (AST) (within the first 24 h) and platelet indices is unclear.

Aim: We investigated the relationship between AST development and platelet indices in acute coronary syndrome patients.

Material and methods: In our case-control study, 33 patients who underwent PCI with subsequent AST development and 59 patients without AST were selected by propensity analysis. We compared the clinical, angiographic, and laboratory data between the AST and control groups.

Results: Mean platelet volume (MPV) ($p = 0.002$) and platelet distribution width ($p = 0.014$) were significantly higher and platelet count ($p = 0.017$) was significantly lower in the AST group. Logistic regression analyses showed that MPV was a significant independent predictor of AST (OR = 1.67; 95% CI: 1.11–2.51; $p = 0.013$). In the ROC analyses, the cut-off value of MPV to detect AST was > 9.1 fl with a sensitivity of 90.9%, a specificity of 42.4%, a positive predictive value of 46.9% and a negative predictive value of 89.3% (AUC: 0.687, 95% CI: 0.582–0.780, $p = 0.001$).

Conclusions: Our study shows that baseline MPV predicts the development of AST in patients with ACS. Mean platelet volume therefore might be an easily accessible marker in the identification of patients at high risk for the development of AST.

Key words: mean platelet volume, acute stent thrombosis, acute coronary syndromes, platelet indices.

Introduction

Percutaneous coronary intervention (PCI) is an effective treatment method that has long been used widely in the treatment of obstructive coronary artery disease [1]. Despite major advances in stent technology and antithrombotic therapy, the development of stent thrombosis continues to be a major problem in patients who have undergone PCI [2]. Most cases of stent thrombosis occur early after PCI, often within a few days. Several factors contribute to the development of stent thrombosis, including the lesion characteristics, procedural factors, patient-related factors, and antiplatelet therapy [3].

Platelets play an important role in the pathogenesis of cardiovascular disease by releasing many mediators involved in inflammation, atherosclerosis, and thrombosis [4]. A relationship between platelet activation in patients with acute coronary syndromes (ACS) and the development of adverse cardiovascular events has been reported [5]. Activation of platelets leads to morphological changes in platelets; more active platelets tend to exhibit a larger volume than do less active platelets [6].

Although a few studies have investigated the relationship between early stent thrombosis and platelet activity, the relationship between acute stent thrombosis (AST) (within the first 24 h) and platelet indices is unclear.

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Aim

In the present study, we investigated the relationship between the development of AST and platelet indices.

Material and methods

In our case-control study, 33 consecutive patients with AST who underwent PCI due to ACS were retrospectively enrolled from January 2012 to March 2014. The control group comprised 59 patients selected from among 2145 patients without AST by using propensity analysis. We compared the clinical, angiographic, and laboratory data between the AST and control groups.

We excluded patients who developed stent thrombosis after the first 24 h, those with a history of hematologic diseases, those with acetylsalicylic acid (ASA) and/or clopidogrel resistance, those in whom TIMI grade 3 flow could not be achieved after PCI, and those who were thought to have edge dissection and/or malpositioning by two experienced interventional cardiologists blinded to the study design. The study was approved by the local Ethics Committee, and informed consent was obtained from all patients.

Patients' baseline clinical and demographic data and previous medical treatments were recorded. Hypertension was defined as a blood pressure of $\geq 140/90$ mm Hg or treatment with antihypertensive medications. Diabetes mellitus was defined as a fasting glucose level of ≥ 126 mg/dl or treatment with oral antidiabetic drugs or insulin. Smokers were defined as current cigarette users or patients who had quit smoking within 1 month of the procedure. Heart failure was diagnosed by transthoracic echocardiography in patients with a left ventricle ejection fraction of $< 40\%$.

All PCI procedures were performed by experienced interventional cardiologists who were blinded to the study design using the femoral artery or radial artery approach as recommended by the current guidelines with a 6- or 7-Fr sheath and 6- or 7-Fr guiding catheter. During PCI, the stent diameter, stent length, stent type, tirofiban use, and pre- and post-dilatation decisions were left to the physician's discretion based on the current literature. Before PCI, 300 mg of oral ASA, 600 mg oral clopidogrel in patients with unstable angina pectoris (UAP)/non-ST elevation myocardial infarction (NSTEMI), 600 mg oral clopidogrel in patients with ST elevation myocardial infarction (STEMI) and 100 IU/kg of intravenous unfractionated heparin (to achieve an activated clotting time > 250 s) were administered to all patients according to the recent guidelines [7, 8]. The type of implanted stent, stent length, stent diameter, and implantation pressure were recorded. A cobalt chromium stent (Tango; MicroPort Medical, Shanghai, China) was used as a bare metal stent (BMS), and a flexible cobalt alloy stent (Endeavor; Medtronic, Minneapolis, MN, USA) was used as drug-eluting stent (DES) in our study. Successful PCI was

defined as residual stenosis of $< 20\%$ and Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the main and side branches with no major complications [8]. Stent thrombosis was defined according to the Academic Research Consortium definition [9]. If the stent thrombosis occurred during the first 24 h, it was defined as AST.

All patients' blood samples were obtained from a peripheral vein immediately before coronary angiography. After the blood samples were obtained, administration of both antiplatelet and antithrombotic drugs was carried out. Blood samples were drawn into standardized tubes containing dipotassium EDTA and evaluated within 30 min to avoid platelet swelling. All hematological measurements were performed using the XT-2000i analyzer (Sysmex Corporation of America, Long Grove, IL, USA).

After PCI, transthoracic echocardiography was performed at the earliest possible time, and the left ventricular ejection fraction was calculated using Simpson's modified biplane method. All echocardiographic measurements were performed using a Vivid 7 GE Medical System (Horten, Norway) with a 3.5-MHz transducer.

Statistical analysis

All analyses were performed using SPSS 19 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as means \pm standard deviation, and categorical variables as percentages. The variables were analyzed using the Kolmogorov-Smirnov test to determine whether they were normally distributed. An independent-samples *t* test was used to compare continuous variables between the two groups. Nonparametric values were compared with the Mann-Whitney *U* test. The χ^2 test was used to compare categorical data. The acute stent thrombosis (+) (AST (+)) and acute stent thrombosis (–) (AST (–)) groups were matched by using propensity analysis in order to preclude biases due to the different distribution of covariates between the groups. The variables including age, gender, hypertension, smoker, diabetes mellitus, hyperlipidemia, diagnosis of MI, tirofiban use and medications, number of stents implanted, target vessel, stent type, diameter and stent length were entered in the propensity model. Afterwards, a one-to-two match between these two groups was obtained by using the nearest-neighbor matching method. To perform the propensity score matching procedure, the PS Matching custom dialogue was used in conjunction with SPSS version 20. The PS Matching program performs all analyses in R through the SPSS-R Plugin (Thoemmes F, 2011) – an SPSS R menu for propensity score matching. [10, 11]. Variables for which the unadjusted *p* value was < 0.10 were identified in multivariate logistic regression analysis as potential risk markers and included in the full model. We reduced the model using multivariate logistic regression analyses with the enter method, and we eliminated potential risk markers using likelihood-ratio tests.

Table I. Clinical and laboratory parameters of the study population according to development of acute stent thrombosis

| Variables | Group 1 AST (-) n = 59 | Group 2 AST (+) n = 33 | Value of p |
|-----------------------------------|------------------------------|------------------------------|---------------|
| Clinical characteristics: | | | |
| Age [years] | 62.15 ±11.72 | 61.15 ±11.50 | 0.694 |
| Gender, male, n (%) | 29 (49.2) | 20 (60.6) | 0.467 |
| DM, n (%) | 16 (27.1) | 9 (27.3) | 0.987 |
| HT, n (%) | 40 (67.8) | 22 (66.7) | 0.912 |
| HPL, n (%) | 34 (57.6) | 22 (66.7) | 0.394 |
| Smoking, n (%) | 25 (42.4) | 17 (51.5) | 0.398 |
| Family history, n (%) | 17 (28.8) | 13 (39.4) | 0.299 |
| Known CAD history, n (%) | 18 (30.5) | 8 (24.2) | 0.522 |
| LVEF (%) | 44.35 ±8.57 | 41.90 ±8.46 | 0.190 |
| Tirofiban usage, n (%) | 8 (13.6) | 9 (27.3) | 0.104 |
| Diagnosis: | | | |
| USAP, n (%) | 9 (15.3) | 3 (9.1) | 0.198 |
| NSTEMI, n (%) | 34 (57.6) | 16 (48.5) | |
| Anterior STEMI, n (%) | 11 (18.6) | 6 (18.2) | |
| Non-anterior STEMI, n (%) | 5 (8.5) | 8 (24.2) | |
| Medications: | | | |
| Statin, n (%) | 22 (37.3) | 11 (33.3) | 0.704 |
| ASA, n (%) | 22 (37.3) | 11 (33.3) | 0.704 |
| BB, n (%) | 17 (28.8) | 8 (24.2) | 0.636 |
| ACEI-ARB, n (%) | 35 (59.3) | 18 (54.5) | 0.657 |
| CCB, n (%) | 16 (27.1) | 11 (33.3) | 0.530 |
| OAD, n (%) | 10 (16.9) | 6 (18.2) | 0.881 |
| Insulin, n (%) | 7 (11.9) | 5 (15.2) | 0.653 |
| Laboratory parameters: | | | |
| Glucose [mg/dl] | 106.94 ±48.10 | 102.75 ±42.79 | 0.687 |
| HDL [mg/dl] | 35.40 ±9.18 | 37.75 ±7.97 | 0.221 |
| LDL [mg/dl] | 129.78 ±46.83 | 111.09 ±39.25 | 0.055 |
| TG [mg/dl] | 168.10 ±86.55 | 181.27 ±114.48 | 0.535 |
| Creatinine [mg/dl] | 1.26 ±0.93 | 1.06 ±0.56 | 0.275 |
| WBC [× 10 ³ /μl] | 11.90 ±3.83 | 11.65 ±3.89 | 0.765 |
| HGB [g/dl] | 13.06 ±1.92 | 13.16 ±2.13 | 0.816 |
| Peak CKMB [ng/ml] | 65.22 ±101.26 | 130.21 ±118.58 | 0.007 |
| Peak troponin [pg/ml] | 893.30 ±1720.16 | 451.76 ±1299.54 | 0.203 |
| PLT count [× 10 ³ /μl] | 289.11 ±72.75 | 251.51 ±67.25 | 0.017 |
| MPV [fl] | 9.52 ±1.32 | 10.39 ±0.97 | 0.002 |
| PDW [fl] | 16.08 ±1.68 | 16.94 ±1.32 | 0.014 |
| PCT (%) | 0.277 ±0.068 | 0.274 ±0.063 | 0.838 |

AST – Acute stent thrombosis, DM – diabetes mellitus, HT – hypertension, HPL – hyperlipidemia, CAD – coronary artery disease, LVEF – left ventricular ejection fraction, USAP – unstable angina pectoris, NSTEMI – non-ST elevation myocardial infarction, STEMI – ST elevation myocardial infarction, ASA – acetylsalicylic acid, BB – β-blocker, ACEI – angiotensin converting enzyme inhibitors, ARB – angiotensin receptor blockers, CCB – calcium channel blockers, OAD – oral anti-diabetics, HDL – high density lipoprotein, LDL – low density lipoprotein, TG – triglyceride, WBC – white blood cells, HGB – hemoglobin, CKMB – creatine kinase-MB, PLT – platelets, MPV – mean platelet volume, PDW – platelet distribution width, PCT – plateletcrit.

In order to demonstrate the cut-off value and the sensitivity and specificity of the mean platelet volume (MPV) in the prediction of AST, receiver operating characteristics (ROC) curve analyses were performed with MedCalc software (Version 12.7.8, Mariakerke, Belgium). A value of $p < 0.05$ was taken to indicate statistical significance.

Results

In the present study, we assessed 92 patients (male, 49 (53.2%)) who underwent PCI with a diagnosis of ACS. The patients were divided into two groups based on the development of AST (group 1, AST (-); group 2, AST (+)). The clinical and hematological characteristics of the study population are shown in Table I. Although the MPV ($p = 0.002$), platelet distribution width (PDW) ($p = 0.014$) and platelet count ($p = 0.017$) were different, the other clinical and hematological parameters were not different between the two groups ($p > 0.05$).

The angiographic parameters of the study population according to the development of AST are presented in Table II. The infarct-related artery, SYNTAX score, and rate of inflation pressure did not differ significantly between the two groups ($p > 0.05$ for all).

The predictors of AST in the multivariable logistic regression analyses are presented in Table III. The effects of variables on AST were calculated using univariate analyses. The variables for which the unadjusted p value was < 0.10 in the logistic regression analysis were identified

Table II. Angiographic characteristics of the study population according to development of acute stent thrombosis

| Variables | Group 1 AST (-) n = 59 | Group 2 AST (+) n = 33 | Value of p |
|--------------------------|------------------------------|------------------------------|---------------|
| Culprit artery, n (%): | | | |
| LAD | 24 (40.7) | 17 (51.5) | 0.418 |
| CX | 20 (33.9) | 7 (21.2) | |
| RCA | 15 (25.4) | 9 (27.3) | |
| SYNTAX Score | 21.52 ±9.36 | 23.34 ±9.65 | 0.378 |
| PCI parameters: | | | |
| DES/total stent ratio | 17/59 | 7/33 | 0.426 |
| Mean stent diameter [mm] | 3.07 ±0.25 | 3.10 ±0.38 | 0.675 |
| Total stent length [mm] | 30.10 ±15.52 | 31.42 ±13.97 | 0.686 |
| Inflation pressure [atm] | 12.80 ±2.55 | 12.23 ±1.55 | 0.245 |
| Mean stent number | 1.52 ±0.70 | 1.63 ±0.74 | 0.479 |
| Predilation, n (%) | 35 (59.3) | 21 (63.6) | 0.684 |

AST – Acute stent thrombosis, IRA – infarct-related artery, LAD – left anterior descending artery, CX – circumflex artery, RCA – right coronary artery, PCI – percutaneous coronary intervention, DES – drug-eluting stent.

Table III. Predictors of acute stent thrombosis in multivariate logistic regression analysis

| Parameters | Univariate analysis | | | Multivariate analysis | | |
|---|---------------------|-----------|------------|-----------------------|------------|------------|
| | OR | 95% CI | Value of p | OR | 95% CI | Value of p |
| Age [years] | 0.99 | 0.96–1.03 | 0.690 | | | |
| Gender, male | 0.74 | 0.32–1.69 | 0.475 | | | |
| Diagnosis* | 1.63 | 0.99–2.68 | 0.055 | 1.39 | 0.79–2.43 | 0.246 |
| Tirofiban usage | 2.39 | 0.82–6.96 | 0.110 | 1.88 | 0.54–6.55 | 0.322 |
| Acetylsalicylic acid usage | 0.84 | 0.34–2.06 | 0.705 | | | |
| PLT count [$\times 10^3/\mu\text{l}$] | 0.99 | 0.98–1.00 | 0.021 | 0.99 | 0.98–1.003 | 0.254 |
| PDW [fl] | 1.45 | 1.07–1.96 | 0.018 | 1.25 | 0.91–1.71 | 0.176 |
| MPV [fl] | 1.84 | 1.23–2.74 | 0.003 | 1.67 | 1.11–2.51 | 0.013 |
| Mean stent length [mm] | 1.01 | 0.98–1.04 | 0.682 | | | |
| Mean stent diameter [mm] | 1.36 | 0.33–5.50 | 0.671 | | | |

PLT – Platelets, MPV – mean platelet volume, PDW – platelet distribution width. *Non-ST elevation myocardial infarction and ST elevation myocardial infarction.

as potential risk markers and included in the full model. MPV (OR = 1.67; 95% CI: 1.11–2.51; $p = 0.013$) was found to be a significant independent predictor of AST in the multivariate logistic regression analysis. The ROC curve analysis used to identify the optimal threshold point of MPV to detect AST in PCI patients is shown in Figure 1. The cut-off value of MPV to detect AST was > 9.1 fl with a sensitivity of 90.9%, a specificity of 42.4%, a positive predictive value of 46.9% and a negative predictive value of 89.3% (AUC = 0.687, 95% CI: 0.582–0.780, $p = 0.001$). Moreover, when we performed logistic regression analysis for the MPV cut-off value of > 9.1 fl obtained by ROC analysis, the value of MPV > 9 fl was 7 times more likely to be observed in AST patients than the patients who did not have AST (OR = 7.04, 95% CI: 2.2–21.8, $p = 0.001$).

Discussion

The main finding of our study is that MPV, with a cut-off value of > 9.1 fl, was an independent predictor of the development of AST although PDW, platelet count, and plateletcrit did not predict AST.

Despite major advances in stenting technology and antiplatelet therapy alternatives, AST remains an important complication of PCI and one of the most important causes of morbidity and mortality [12]. More than 80% of cases of angiographically confirmed stent thrombosis occur within 2 days after PCI regardless of the stent type (BMS or DES) [9, 12]. Many factors can contribute to the development of AST, including patient characteristics, lesion characteristics, and procedural factors [13]. Activated platelets play an important role in the pathogenesis and progression of ACS [14]. Antithrombotic therapy is known to reduce ischemic complications after PCI in patients with ACS [15]. Despite advances in antiplatelet treatment, studies have shown that higher platelet

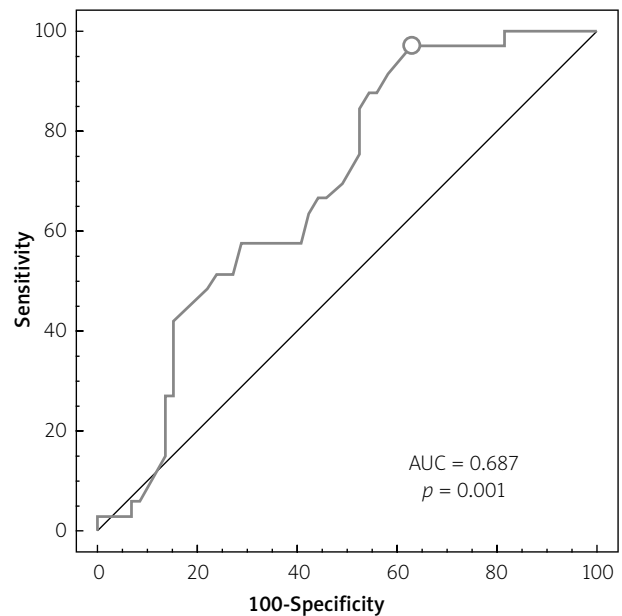


Figure 1. ROC curve analysis used to identify the optimal threshold point of MPV in the detection of AST in PCI patients. The area under the ROC curve was 0.687. The optimal threshold point of AST was > 9.1 fl (AUC = 0.687, 95% CI: 0.582–0.780, $p = 0.001$)

reactivity both residual and on treatment increases the incidence of cardiovascular events during the treatment and follow-up periods [16, 17]. Many tests are used to assess platelet reactivity. In recent studies, platelet indices have been shown to reflect the degree of platelet reactivity. For example, larger platelets have more prothrombotic materials and GpIIb–IIIa receptors than do smaller platelets. Thus, larger platelets are more active in terms

of metabolic and enzymatic properties than are smaller platelets [18, 19].

Platelet indices predict short- and long-term adverse events in patients with stroke and ACS as well as during the post-PCI period [20, 21]. We previously found that higher MPV and PDW were correlated with thrombolysis failure in patients with STEMI treated with thrombolytic therapy [22]. Huczek *et al.* also reported that platelet indices, especially MPV, predicted impaired reperfusion, long-term mortality, and the development of stent thrombosis within 30 days [23, 24]. The current study may be considered to be similar to that of Huczek *et al.*, but the two studies also differ in some respects. First, while their study group comprised patients who developed early stent thrombosis within a few days, only a few of whom developed AST (14%), we excluded patients with subacute stent thrombosis in our study, focusing only on AST that occurred within the first 24 h. Second, they used only a BMS during PCI, but both a BMS and a DES were used in our study.

As a potent antithrombotic agent, tirofiban inhibits platelet aggregation and reduces the incidence of ischemic events by binding to GpIIb–IIIa receptors [25, 26]. Due to our study design we did not find a significant difference between the two groups. Clopidogrel and ASA resistance also contributes to AST, but the relationship between clopidogrel resistance and baseline platelet indices remains unclear. Tanboğa *et al.* found no correlation between clopidogrel resistance and MPV or PDW [27]. For ethical reasons, we did not assess the relationship between clopidogrel/ASA resistance and platelet indices in patients with AST in the present study.

Despite the case-control study design, our study had several limitations. The first was the limited sample size and single center trial. Second, we could not perform clopidogrel and/or ASA resistance tests, which investigate whether the development of acute stent thrombosis originates due to ASA or clopidogrel resistance. Third, intravascular ultrasound is not routinely performed in our clinic, so we could not exclude patients with dissection or stent malpositioning, which might not be visible in angiography. Due to these limitations, our study should be supported by cohort studies.

Conclusions

In conclusion, an MPV value of > 9.1 fl could predict acute stent thrombosis; thus we think that patients with MPV above this value should be followed more closely and take more aggressive antiplatelet therapy to avoid acute stent thrombosis in patients with acute coronary syndrome. Therefore, MPV might be an easily accessible marker in the identification of patients at high risk for the development of AST.

Conflict of interest

The authors declare no conflict of interest.

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