

Original
Article

Factors Associated with Low Admission Platelet Count in Adults with Acute Aortic Dissection

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Purpose: Platelets are crucial components of the coagulation processes, and low admission platelet count (PLC) is associated with adverse clinical outcomes in patients with Stanford type A acute aortic dissection (AAD).

Methods: A total of 130 consecutive patients undergoing Stanford type A AAD surgery in Beijing Anzhen Hospital were enrolled between January 2013 and July 2014. Preoperative clinical and laboratory data from patients were collected. Multiple regression analyses were used to determine the independent factors of low admission platelets.

Results: Adjusted multiple regression analysis showed that age (β : -1.069 , 95% confidence interval [CI]: $-2.109, -0.029$), sex (β : -29.973 , 95% CI: $-56.512, -3.433$), tissue factor pathway inhibitor (TFPI; β : 0.197 , 95% CI: $0.039, 0.354$), fibrinogen degradation product (FDP) (β : -0.476 , 95% CI: $-0.879, -0.074$), and attack time (β : 11.125 , 95% CI: $7.963, 14.287$) were significantly associated with admission PLC. Admission PLC increased with attack time up to the 3 days (β : 16.2 , 95% CI: $12.1, 20.2$).

Conclusions: We found that increasing age, male patients, patients with lower serum levels of TFPI and higher serum levels of FDP, and patients with a shorter attack time were significantly associated with lower PLC at admission. Moreover, the turning point of attack time is 3 days after the onset of dissection.

Keywords: platelet count, acute aortic dissection, multiple regression analysis, admission

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Introduction

Stanford type A acute aortic dissection (AAD) represents a serious cardiovascular disease with a high mortality and morbidity.^{1–4} The period of 14-day after onset has been designated the acute phase, with a mortality rate of 1%–2% per hour early after symptom onset.⁵ Blood flow through the false lumen is a powerful activator of platelets and the coagulation/fibrinolytic system. Decreased platelet function and platelet count (PLC) have been observed in patients with type A AAD.^{6,7} It has been proposed that a reduction in PLC might correlate with the excessive consumption of platelets in response to thrombosis of the false lumen during AAD. Moreover, platelet activation in AAD can activate

attached leukocytes and induce further activation of endothelial cells by releasing pro-inflammatory mediators in response to more severe ischemia-reperfusion injury and systemic inflammation.⁸⁻¹⁰ Therefore, it is reasonable to speculate that the reduced PLCs are associated with adverse clinical outcomes.¹¹ Recently, accumulating evidence has demonstrated that PLC is positively associated with survival.^{7,12} However, the factors related to PLC upon admission have not been clarified in patients with type A AAD. Thus, the aim of this study was to evaluate the factors related to low admission PLC in patients with type A AAD.

Methods

Study design and population

This study was a retrospective analysis of prospectively collected data, which resulted from a previous clinical trial (ClinicalTrials.gov, Identifier: NCT01894334) and full details of the methods have been previously published¹³ and were approved by the Beijing Anzhen Hospital Clinical Research Ethics Committee (Identifier: 2012013). Patients with Stanford type A AAD were eligible if they were 18- to 75-years old and were suitable for emergency surgery. A total of 130 consecutive patients undergoing Stanford type A AAD surgery in Beijing Anzhen Hospital were enrolled between January 2013 and July 2014. All of the patients enrolled in this study had normal hepatic and renal function. Exclusion criteria included patients with coronary heart disease, heart failure, severe cardiac tamponade, unstable hemodynamics, nervous system abnormalities, and clinically apparent malperfusion.¹⁴ In brief, all cases were class Aa according to the Penn Classification,¹⁵ which is the absence of branch vessel malperfusion or circulatory collapse. Patients prescribed non-steroidal anti-inflammatory drugs or corticosteroids before or after admission were also excluded.¹³

Data collection

The investigators and the participants were not informed of the results during the study. The data were collected through assessments using the data collection protocol.¹³ In brief, demographics and etiology, such as Body Mass Index (BMI), regular use of prescription drugs, smoking history, hypertension history, and diabetes history, were recorded at recruitment. The onset time of sudden severe chest or upper back pain, loss of consciousness, shortness of breath, sudden difficulty speaking, loss of vision, and weakness or paralysis of one side of the body

were recorded. The attack time was defined as the time between disease onset and urgent surgery. At admission, hemodynamic performance, echocardiographic data, and EuroSCORE values were recorded. Venous blood samples were drawn, centrifuged, and stored at -70°C until subsequent use. Plasma levels of interleukin-6 (IL-6), IL-10, tissue factor (TF), tissue factor pathway inhibitor (TFPI), human leukocyte elastase (HLE), tumor necrosis factor alpha (TNF α), vascular endothelial growth factor (VEGF), prostaglandin I₂ (PGL₂), and thromboxane B₂ (TXB₂) were assayed by enzyme-linked immune absorbent assay according to the manufacturer's instructions (Multiskan MK3 Automatic microplate reader, Thermo Fisher Scientific, Waltham, MA, USA). Methane dicarboxylic aldehyde (MDA), myeloperoxidase (MPO), total anti-oxidation capacity (TAOC), and total superoxide dismutase (TSOD) were evaluated by ultraviolet-visible spectroscopy. PLC, hemoglobin (Hb), white blood cell (WBC), lactic acid (LAC), fibrinogen (FIB), and fibrinogen degradation product (FDP) were determined by standard quantitative assay techniques in the hospital's Clinical Laboratory Center.

Patient and public involvement

Patients were not involved in the development of the research question, the design, recruitment, or conduct of this study. Patients who participated did so anonymously, and therefore the study team will be unable to disseminate the results to study participants.

Outcomes

The primary outcomes were independent factors correlating with admission PLC in patients with type A AAD. Additionally, variation in preferences for demographics and etiology characteristics (e.g., gender, age), hemodynamic performance (e.g., blood pressure, heart rate), and serological results at admission (e.g., IL-6, TFPI, TNF α , and TXB₂) were also assessed.

Statistical analysis

All data analyses were performed with EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston, MA, USA) and R software (http://www.R-project.org). Quantitative variables were presented as the mean \pm standard deviation or median (interquartile range [IQR]), and categorical variables were presented as frequencies or percentages. Univariate and multiple regression analyses were used to determine the independent factors of admission PLC. In univariate analysis, variables associated

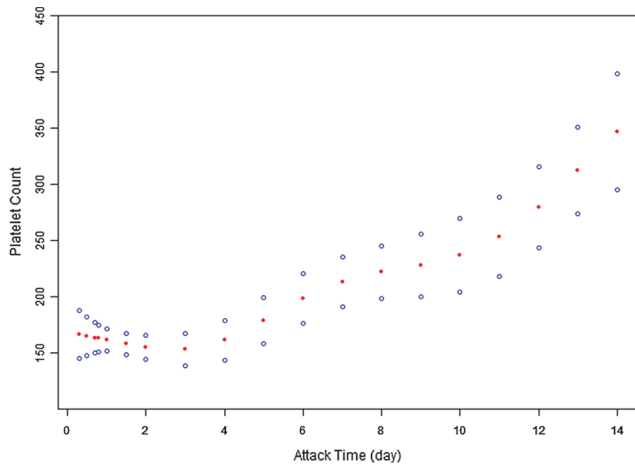


Fig. 1 A nonlinear relationship between attack time and admission platelet count in Chinese adults with Stanford type A acute aortic dissection after adjustment for age, sex, and smoking history.

with admission PLC with a p value < 0.10 were selected. Then, these selected variables were used in multiple regression analyses to estimate the β coefficient for admission PLC and their corresponding 95% confidence intervals (CIs). Smoothing spline plots of independent factors related to admission PLC were created, and threshold effect analysis of independent factors on PLC was performed. p values less than 0.05 were considered statistically significant.

Results

The flow diagram is present in **Supplemental Fig. 1**. (The supplementary material is available at ATCS online.) According to inclusion and exclusion criteria, a total of 130 patients undergoing Stanford type A AAD surgery were ultimately included in this study. The mean age of all of the patients was 46.8 years (range, 21–72 years), and the majority of patients were male (75.4%). Baseline characteristics are presented in **Table 1**. Univariate analysis showed that the nine variables, including Age, Sex, BMI, History of smoking, Attack time, WBC, FDP, TFPI, and TXB2 were associated with admission PLC (**Table 1**). Multiple regression analyses of these variables showed that age (β : -1.069 , 95% CI: -2.109 , -0.029 , $p = 0.0462$), sex (β : -29.973 , 95% CI: -56.512 , -3.433 ; $p = 0.0289$), plasma levels of TFPI (β : 0.197 , 95% CI: 0.039 , 0.354 ; $p = 0.0158$), plasma levels of FDP (β : -0.476 , 95% CI: -0.879 , 0.074 ; $p = 0.0221$), and attack time (β : 11.125 , 95% CI: 7.963 , 14.287 ; $p < 0.0001$) were significantly associated with admission PLC with or without adjusting for factors

(**Table 2**). After adjusting for conventional clinical factors, a nonlinear relationship between attack time and admission PLC was observed (**Fig. 1**). The admission PLC increased with increasing attack time up to the 3 days (turning point) (β : 16.2 , 95% CI: 12.1 , 20.2 ; $p < 0.001$) (**Table 3**).

Discussion

The present study showed what independent factors correlate with admission PLC in patients with Stanford type A AAD. Specifically, increasing age, male patients, patients with lower serum levels of TFPI and higher serum levels of FDP, and patients with a shorter attack time were significantly associated with lower PLC at admission. After adjusting for age, sex, and smoking history, a U-shaped association between attack time and PLC was observed and a longer attack time (≥ 3 days) was associated with higher PLC.

A low PLC at admission could reflect a consumption process second to inflammation and thrombosis in AAD. Patients with a greater extent of dissection associated with a lower PLC and higher serum C-reactive protein (CRP) in AAD could account for this hypothesis.⁹ Huang et al.¹² found that low admission PLC was significantly associated with higher in-hospital mortality in patients with type A AAD. Consistent with these results, in our previous study,¹⁶ lower preoperative PLC was a risk factor for prolonged mechanical ventilation (PMV) after type A AAD surgery, which associated with increased in-hospital mortality and decreased 1-year survival rate compared with the non-PMV group.

More recently, it has been reported that PLC decreases during aging, and is higher in women than in men.¹⁷ In The Moli-sani Study, 21,635 subjects were recruited and consistent associations with low PLC and higher risk for total mortality were found.¹⁸ The Moli-sani Study evaluated the association of age- and sex-specific ranges of PLC with the risk of all-cause mortality in a large population-based epidemiologic cohort. In the present study, we found that the PLC in patients with AAD decreased 1.069 ($10^9/L$) with each 1-year increase in age, and female PLC exceeded those of men by 29.973 ($10^9/L$). The decrease in PLC in the elderly may reflect a reduction in hematopoietic stem cell reserve or in the quality of the individual stem cells that occurs during aging.¹⁹ Another finding of our study concerns gender-related differences in PLC in patients with AAD. The reduction of body iron in menstruating women is probably related to their higher PLC because platelet

Table 1 Baseline characteristics of patients and univariate regression analysis for admission platelet count

Variables	Characteristics	Univariate analysis	
		β (95% CI)	p value
Number (n)	130		
Age (year)	46.86 \pm 10.52	-1.166 (-2.287, -0.045)	0.0436
Sex			
Females, n (%)	32 (24.615)	1	
Males, n (%)	98 (75.38)	-30.126 (-57.347, -2.905)	0.0319
BMI (kg/m ²)	25.90 \pm 3.44	0.567 (-2.883, 4.017)	0.7478
History of smoking, n (%)	66 (50.77)	-20.098 (-43.725, 3.528)	0.0979
History of hypertension, n (%)	94 (72.31)	-0.518 (-27.200, 26.163)	0.9697
History of DM, n (%)	4 (3.08)	47.452 (-21.194, 116.099)	0.1778
Attack time (d)	2.00 (1.00–5.00)	11.229 (8.266, 14.193)	<0.0001
Preoperative SBP (mm Hg)	113.24 \pm 18.24	0.106 (-0.555, 0.766)	0.7537
Preoperative DBP (mm Hg)	56.02 \pm 11.89	0.059 (-0.954, 1.073)	0.9090
LVEF (%)	62.58 \pm 8.39	-0.636 (-2.070, 0.798)	0.3863
LVEDD (mm)	51.40 \pm 7.47	0.953 (-0.685, 2.591)	0.2564
EuroSCORE [#]	5 (5, 6)	-3.831 (-14.966, 7.304)	0.5013
3 n (%)	19 (14.62)	-	
4 n (%)	5 (3.85)	-	
5 n (%)	69 (53.08)	-	
6 n (%)	30 (23.08)	-	
7 n (%)	5 (3.85)	-	
8 n (%)	2 (1.54)	-	
Aortic regurgitation (n=129)			
Non-regurgitation n (%)*	27 (20.93)	1	
Mild-regurgitation n (%)	52 (40.31)	18.137 (-14.242, 50.517)	0.2744
Moderate-regurgitation n (%)	22 (17.05)	4.008 (-35.197, 43.213)	0.8415
Severe-regurgitation n (%)	28 (21.71)	5.930 (-30.888, 42.748)	0.7528
Serum variables			
Hb (g/L)	12.80 (11.90–13.50)	0.342 (-0.748, 1.432)	0.5399
WBC (10 ⁹ /L)	9.44 (7.54–10.82)	-3.319 (-6.834, 0.197)	0.0666
LAC (mmol/L)	1.00 (0.80–1.40)	-8.312 (-20.265, 3.642)	0.1753
Coagulation/fibrinolysis			
FIB (g/L)	3.78 (2.85–4.62)	4.718 (-3.982, 13.418)	0.2899
FDP (mg/L)	10.20 (6.20–18.70)	-0.831 (-1.305, -0.358)	0.0008
PAI-1 (ng/mL)	0.71 \pm 0.19	-5.119 (-67.795, 57.557)	0.8731
TF (ng/mL)	3.48 (2.62–4.88)	0.293 (-4.546, 5.133)	0.9056
TFPI (ng/mL)	146.42 \pm 65.20	0.257 (0.079, 0.436)	0.0054
Inflammatory			
IL-6 (pg/mL)	56.19 (46.47–70.50)	0.170 (-0.353, 0.693)	0.5247
IL-10 (pg/mL)	78.38 (43.68–114.85)	0.176 (-0.029, 0.380)	0.0946
HLE (ng/mL)	2.23 (1.67–2.63)	3.457 (-6.048, 12.961)	0.4772
TNF α (pg/mL)	53.77 (38.61–70.78)	0.091 (-0.295, 0.478)	0.6444
ROS			
MDA (nmol/mL)	3.30 \pm 0.59	-12.927 (-33.006, 7.151)	0.2093
MPO (units/L)	46.93 \pm 15.01	0.541 (-0.269, 1.350)	0.1932
TAOC (units/mL)	7.17 \pm 1.87	.713 (-2.659, 10.085)	0.2555
TSOD (units/mL)	109.15 \pm 42.86	0.058 (-0.231, 0.347)	0.6964
Platelet and endothelial cell			
Platelet count (10 ⁹ /L)	168.77 (136.25–204.00)	-	
VEGF (pg/mL)	198.92 (135.86–338.26)	-0.012 (-0.068, 0.044)	0.6757
PGI ₂ (pg/mL)	49.69 (25.19–103.20)	0.026 (-0.098, 0.150)	0.6807
TXB ₂ (pg/mL)	154.82 \pm 98.94	-0.120 (-0.240, -0.001)	0.0502

Data are given as numbers, percentage, mean \pm standard deviation or median IQR. *: Non-regurgitation group is the reference group. #: EuroSCORE is defined as continuous variable. BMI: Body Mass Index; CI: confidence interval; DM: diabetes mellitus; DBP: upper limb diastolic blood pressure; EuroSCORE: European system for cardiac operative risk evaluation; FDP: fibrinogen degradation product; FIB: fibrinogen; Hb: hemoglobin; HLE: human leukocyte elastase; IL: interleukin; LAC: lactic acid; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; MDA: methane dicarboxylic aldehyde; MPO: myeloperoxidase; PGI₂: prostaglandin I₂; PLC: platelet count; ROS: reactive oxygen species; SBP: upper limb systolic blood pressure; TAOC: total anti-oxidation capacity; TSOD: total superoxide dismutase; TF: tissue factor; TFPI: tissue factor pathway inhibitor; TNF α : tumor necrosis factor α ; TXB₂: thromboxane B₂; VEGF: vascular endothelial growth factor; WBC: white blood cells; IQR: interquartile range; PAI-1: plasminogen activator inhibitor-1

Table 2 Multivariate regression analysis for admission platelet count with or without adjustment (n = 124)

Exposure	Crude model	Multivariate-adjusted model 1	Multivariate-adjusted model 2
	β (95% CI) p value	β (95% CI) p value	β (95% CI) p value
Sex			
Females*	1	1	1
Males	-31.579 (-54.433, -8.724) 0.0078	-30.19 (-56.603, -3.778) 0.0270	-29.973 (-56.512, -3.433) 0.0289
Age (per 1 year)	-1.181 (-2.159, -0.203) 0.0196	-1.162 (-2.160, -0.164) 0.0243	-1.069 (-2.109, -0.029) 0.0462
TFPI (per 1 ng/mL)	0.229 (0.085, 0.373) 0.0023	0.228 (0.083, 0.373) 0.0025	0.197 (0.039, 0.354) 0.0158
FDP (per 1 mg/L)	-0.476 (-0.874, -0.078) 0.0208	-0.476 (-0.876, -0.077) 0.0212	-0.476 (-0.879, -0.074) 0.0221
Attack time (per 1 day)	10.492 (7.626, 13.357) <0.0001	10.493 (7.616, 13.37) <0.0001	11.125 (7.963, 14.287) <0.0001

Crude: no adjustment. Model I: adjusted for history of smoking. Model II: adjusted for history of smoking, TXB₂, IL-10, and WBC.

*: Females group is the reference group. CI: confidence interval; TFPI: tissue factor pathway inhibitor; FDP: fibrinogen degradation product; TXB₂: thromboxane B₂; IL: interleukin; WBC: white blood cells

Table 3 Threshold effect analysis of attack time and platelet count in Chinese adults with Stanford type A acute aortic dissection after adjustment for age, sex, and smoking history

Exposure: attack time (day)	Platelet count (10 ⁹ /L) ^a
Model I	
One line slope	10.9 (8.0, 13.8) <0.001
Model II	
Turning point (K)	3
< K slope 1	-8.8 (-20.2, 2.7) 0.136
> K slope 2	16.2 (12.1, 20.2) <0.001
Slope 2-Slope 1	24.9 (10.8, 39.0) 0.001
Predicted at K	144.0 (125.6, 162.5)
LRT test	0.001
95% CI of K	1.4875, 11

^aAdjusted for age, sex and history of smoking. Results in table: β (95% CI) p value. LRT test: likelihood-ratio test; CI: confidence interval

production is stimulated by moderate iron deficiency.^{20,21)} However, hormonal differences between men and women could also be involved, as estrogens were shown to favor platelet formation *in vitro* and *in vivo*.²²⁾ During the progress of AAD, there is a significant correlation between inflammation and platelet activation, which may be induced by a tear in the aortic wall and exposed collagen.^{9,23)} Therefore, there was a more profound effect on age- and sex-specific PLC in patients with AAD.

In this study, TFPI level was positively correlated with PLC, but FDP level was negatively correlation with PLC, indicating that PLC was modulated by active coagulation and fibrinolytic systems. During the progress of AAD, blood flow through the nonendothelialized false lumen and turbulence formation is a powerful activator of the coagulation and fibrinolytic systems.²⁴⁾ The hemostatic system is activated, resulting in clotting factor consumption and ultimately coagulopathy, leading to intense activation of fibrinolysis by fibrin formation and degra-

dation. TFPI regulates the extrinsic pathway of blood coagulation to inhibit either TF²⁵⁾ or early forms of prothrombinase. It is also essential for the dampening of thrombin-mediated platelet activation,²⁶⁾ which decreases platelet consumption to elevate PLC. FDP is the degradation product of fibrous protein by plasmin, which participates in the development and progression of atherosclerosis and thrombus, and is positively correlated with the possibility of thrombosis type AAD.²⁷⁾ In 1991, Winters et al.²⁸⁾ found that plasmin-derived FDPs could promote platelet aggregation in response to activation with various agonists, which increased platelet consumption to reduce PLC.

The current study shows that in the interval between dissection onset and surgery, there is a time-dependent effect on PLC, which revealed that admission PLC increased 16.2 (10⁹/L) by a 1-d increase in attack time up to 3 days. Thus, there is a reasonable prospect of getting the pathophysiology changes as the progress of AAD. Xu et al.²⁹⁾ reported that there was evidence of adventitial

inflammation, such as neutrophils peaking at 24 h, mitotic figures at 28 h, apoptotic bodies at 60 h, and eosinophils at 23 h in 40 aortas. Albini et al.³⁰⁾ also reported that D-dimer levels significantly increased after dissection onset and then dropped after 2 days, but still remained elevated over a 10-d period in AAD patients.

Study Limitations

This study had several limitations. First, it was conducted at only one university center, and the number of cases was relatively small for a relatively short period time. Second, the time of the initiating event was chosen by necessity as the onset of pain. It is quite possible that the initiation of the intimal tear may predate that of the dissection itself with pain or painless. Thus, the attack time does not accurately reflect the time between dissection onset and surgery. Third, all of the patients in our study were suitable for emergency AAD surgery without severe malperfusion and unstable hemodynamics, which are not representative of all patients. Forth, Stanford type A AAD demonstrated the similar volume of aortic dissection; however, we were not able to obtain highly detailed information to evaluate the volume of false lumen and thrombogenesis. Finally, it is not yet clear that there is any true cause-and-effect relationship between independent factors and PLC for the cross-sectional study. Therefore, a large cohort study is recommended to address these problems.

Conclusion

The present study found that increasing age, male patients, patients with lower serum levels of TFPI and higher serum levels of FDP, and patients with a shorter attack time were significantly associated with lower PLC at admission. Moreover, the turning point of attack time is 3 days after the onset of dissection.

Ethics Approval and Consent to Participate

This study was in agreement with the guidelines of the Ethics Committee of the Beijing Anzhen hospital. All patients gave verbal and written informed consent prior to enrollment.

Contributors

MJ was responsible for the original idea, which was co-developed by all authors. All authors (SWL, JKL,

WPC, JMZ, and MJ) developed the conception and design of this manuscript. JKL, WPC, and JMZ validated the provision of study materials or patients and SWL carried out all the data management and statistical analyses, which was supervised by MJ. SWL and MJ were responsible for writing the manuscript, which was critically revised by all coauthors.

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Data Sharing Statement

The dataset used and analyzed during the current study are available from the corresponding author upon reasonable request.

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Disclosure Statement

All authors have no conflict of interest.

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