

# Prognostic Value of Platelet-to-Platelet Distribution Width Ratio in Postoperative Patients with Type A Acute Aortic Dissection

Yaman Wang, BA,<sup>1,2\*</sup> Xiaohong Xia, BA,<sup>1,2\*</sup> Qing Li, MD,<sup>1,2\*</sup> Gaoxia Ge, MD,<sup>1,2</sup> Jun Zhou, MD<sup>1,2</sup>

<sup>1</sup>Department of Laboratory Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China;

<sup>2</sup>Branch of National Clinical Research Center for Laboratory Medicine, Nanjing, China

## ABSTRACT

**Objective:** Acute type A aortic dissection (AAD) is a serious life-threatening cardiovascular emergency with high in-hospital mortality without aggressive clinical treatment. The study intended to identify the relationship between platelet (PLT) to platelet distribution width (PDW) ratio (PPR) and in-hospital mortality in postoperative patients with type A AAD.

**Methods:** A total of 171 type A AAD patients were recruited in this retrospective study from January 2017 to December 2019. Receiver operating characteristics (ROC) were exploited to determine the best cut-off value of PPR, and then patients were sub-grouped into the low-PPR group and high-PPR group, according to the optimal value of PPR. Finally, univariate, and multivariate analyses were carried out to examine the prognostic value of PPR.

**Results:** The value of PPR was 9.76, and the mortality was statistically higher in the low-PPR group than in the high-PPR group (29.1% vs. 6.0%,  $P < 0.01$ ). The area under the ROC curve (AUC) of PPR was 0.724 (95% CI, 0.633-0.815;  $P < 0.001$ ) with a 56.4% sensitivity and 80.6% specificity. Multivariate analysis showed that serum PPR was an independent factor associated with in-hospital mortality (hazard ratio (HR): 1.151; 95% confidence interval (CI): 1.035 -1.297;  $P = 0.010$ ).

**Conclusion:** Serum PPR can be used as an independent predictor of in-hospital mortality in postoperative patients with type A AAD.

two types: type A and type B. Type A AAD is a critical life-threatening cardiovascular emergency as the ascending aorta is involved. Without aggressive clinical treatment, its initial mortality rate is 33% within 24h and 50% within 48h [De Leon 2012]. Thus, type A AAD requires timely diagnosis and surgical intervention [Carnevale 2011; Gao 2019]. However, at the initial examination, the diagnosis of AAD is neglected up to 38%, while 28% of patients are first diagnosed with AAD through a post-mortem examination [Tsai 2009]. Therefore, it is crucial to identify high-risk AAD patients at an early phase.

AAD is related to an inflammatory response, thrombosis, and oxidative stress, which is accompanied by significantly elevated inflammatory indexes, for example, C-reactive protein (CRP), D-dimer, and platelets (PLT) [Du 2017; Li 2017; Li 2016; Li 2016]. However, these indicators are low either in sensitivity, specificity, or in diagnostic efficacy. Therefore, more indicators are needed to identify the high-risk AAD patients.

PLT take an important part in the processes of physiology and pathology. PLT and PLT parameters can be used as markers of inflammation. Previous study has shown that PPR is elevated in adult-onset Still's disease patients [Liu 2019]. However, no research on PPR is obtainable in the prognosis of patients with aortic dissection. Therefore, the primary goal of this study was to examine the value of serum PLT to PDW(PPR) in predicting in-hospital mortality in patients with type A AAD.

## INTRODUCTION

Aortic dissection is a tear located within the intimal layer of the aortic wall that causes blood to flow into the tunica media [Nienaber 2016]. Acute aortic dissection (AAD) consists of

## MATERIALS AND METHODS

**Study design:** A retrospective and single-center investigation were designed to evaluate the association between PPR and the risk of in-hospital mortality in postoperative patients with type A AAD. A total of 171 patients with type A AAD were enrolled between January 2017 and December 2019, in The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China. Type A AAD patients were verified by a multidetector computed tomography scan. The included patients fulfilled the following criteria: type A AAD within 24 hours after symptom onset, surgical intervention, and age over 18 years. The exclusion criteria were as follows: (1) pregnancy; (2) trauma induced AAD; (3) patients with infection, cancers, and other diseases related to the cardiovascular, urinary, endocrine, and immune systems. Clinical

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\*Yaman Wang, Xiaohong Xia and Qing Li contribute to this work equally.

Correspondence: Jun Zhou, Department of Laboratory Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China, Telephone +862568303450 (e-mail: zhoujun5958@163.com), and Gaoxia Ge, Department of Laboratory Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China, Telephone +862568308020 (e-mail: gegaoxia@126.com).

information, including the demographic profile, admission hematologic laboratory data (Sysmex XE 2100, Kobe, Japan), and the results of the CT scan were obtained from the medical record. Clinical outcomes were obtained from the medical record or telephone results. The study was authorized by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (Nanjing, China) and was in line with the Helsinki Declaration (2021-SR-529).

**Endpoint:** The endpoint of the study was all-cause in-hospital mortality within 30 days.

**Statistical analysis:** SPSS 21.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. We used the receiver operating characteristic (ROC) curve to calculate the cut-off values for PPR and determine the cut-off value for PPR in predicting in-hospital mortality. Additionally, we performed chi-square and Mann-Whitney U-tests to determine statistically significant differences between the low-PPR group and high-PPR group. Results are displayed as mean  $\pm$  standard deviation (SD). Furthermore, variables with a marginal association with mortality ( $P < 0.10$ ) were entered in a stepwise multivariable logistic regression model for in-hospital mortality. Multivariate binary logistic regression analyses (forward-LR method) were performed to identify the predictors of in-hospital mortality. The hazard ratio (HR) and the 95% confidence interval (CI) also were calculated. A value of  $P < 0.05$  was considered significant.

## RESULTS

Optimal cut-off values and patients' stratification: ROC was introduced to fix the optimal cut-off values for PPR. The results exhibited that the optimal cut-off value of PPR was 9.76. Moreover, the AUC of PPR was 0.726. (Figure 1) Consequently, participants with  $PPR \geq 9.76$  were placed into the high group, whereas those with a lower value were stratified into the low group.

The baseline characteristics and laboratory results of the study patients' characteristics and indexes of patients are depicted in Table 1. (Table 1) The median age of participants in our study cohort was 53 years, and 77.0% of all enrolled patients were male. The mean age of the low-PPR group was higher than that of the high-PPR group, which was statistically significant ( $57 \pm 11.80$  vs.  $50 \pm 11.85$ ,  $P < 0.001$ ). The results indicated that patients with advanced age had a worse prognosis after surgery in the hospital. Compared with the low-PPR group, the value of serum red blood cell distribution width (RDW), mean platelet volume (MPV), and platelet distribution width (PDW) were significantly decreased in the high-PPR group (all  $P < 0.05$ ). The levels of serum PLT, plateletcrit (PCT), PLT to RDW ratio (PRR), PLT to MPV ratio (PMR), and PLT to hemoglobin (HB) ratio (PHR) were significantly higher in the high-PPR group than in the low-PPR group (all  $P < 0.05$ ). There were no significant statistical differences in serum whole blood counts (WBC), lymphocytes, neutrophils, and HB ( $P > 0.05$  for all). Furthermore, we found that the mortality of patients in the low-PPR group was higher than that of the high-PPR group ( $P < 0.001$ ).

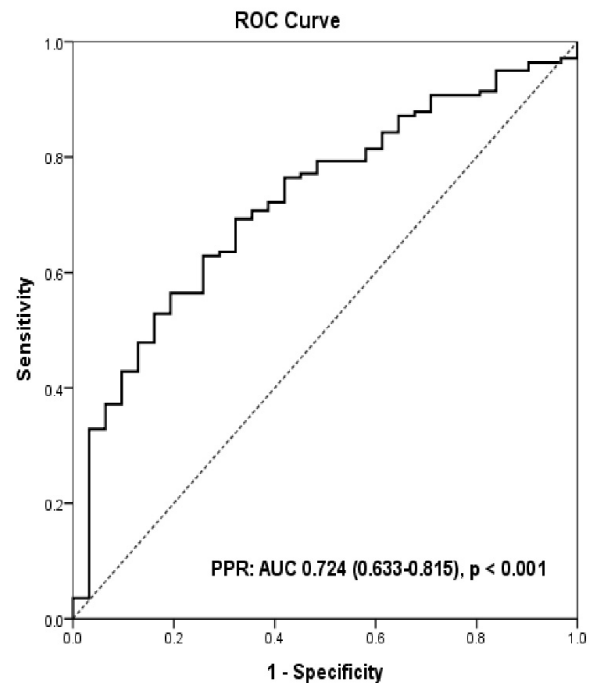


Figure 1. Receiver operating characteristic (ROC) curve of PPR for predicting in-hospital mortality in postoperative patients with type A AAD.

**Multivariate logistic regression:** Variables with a  $P$  value  $\leq 0.10$  in univariable analysis were selected into a multivariate logistic regression model to check whether these variables were independent factors to predict in-hospital survival of type A AAD patients. Multivariate analysis demonstrated that age (HR 0.931; 95% CI, 0.905-0.979;  $P = 0.003$ ) and PPR (HR 1.151; 95% CI, 1.035-1.297;  $P = 0.01$ ) were independent predictors to predict the outcome of type A AAD patients. (Table 2) Thus, PPR is an independent risk factor to predict in-hospital mortality for postoperative patients with type A AAD.

## DISCUSSION

This study showed that PPR is a useful and independent predictor of in-hospital mortality in postoperative patients with type A AAD. Those with high admission PPR had low in-hospital mortality. These findings suggested that PPR can be used as a useful clinical marker to identify high-risk type A AAD patients.

Thrombosis is a pathological process of aortic dissection [Akutsu 2005]. PLT acts as a key part of physiological and pathological processes, such as coagulation, thrombosis, inflammation, and maintenance of the integrity of vascular endothelial cells [Gardiner 2014; Gasparyan 2011; Golebiewska 2015]. After aortic rupture, PLT is the first cellular component to be recruited and adhere to the damaged vessel, followed by white blood cells, and form a thrombus in the false lumen [Zhang 2014]. Then, activated PLT may secrete pro-inflammatory cytokines to initiate inflammatory responses in the setting of aortic dissection [Le 2015; Semple

Table 1. Clinical characteristics of the study population

| Variables                      | Total (N = 171)    | Low-PPR (N = 86)   | High-PPR (N = 85)  | P-value |
|--------------------------------|--------------------|--------------------|--------------------|---------|
| Age (years)                    | 53 (24-86)         | 57 (26-86)         | 50 (24-79)         | <0.001  |
| Male (N, %)                    | 131 (77%)          | 68 (79%)           | 63 (74%)           | 0.473   |
| WBC ( $\times 10^9/L$ )        | 11.45 $\pm$ 3.60   | 11.39 $\pm$ 3.76   | 11.72 $\pm$ 3.45   | 0.580   |
| Lymphocyte ( $\times 10^9/L$ ) | 0.88 $\pm$ 0.62    | 0.82 $\pm$ 0.69    | 0.93 $\pm$ 0.53    | 0.259   |
| Neutrophil ( $\times 10^9/L$ ) | 9.90 $\pm$ 3.33    | 9.81 $\pm$ 3.44    | 10.02 $\pm$ 3.25   | 0.723   |
| HB (g/L)                       | 124.38 $\pm$ 18.45 | 122.02 $\pm$ 18.52 | 126.79 $\pm$ 18.29 | 0.093   |
| RDW                            | 13.75 $\pm$ 1.47   | 14.23 $\pm$ 1.76   | 13.27 $\pm$ 0.91   | <0.001  |
| PLT ( $\times 10^9/L$ )        | 134.09 $\pm$ 62.54 | 91.12 $\pm$ 29.09  | 176.65 $\pm$ 57.52 | <0.001  |
| PCT (%)                        | 0.14 $\pm$ 0.06    | 0.10 $\pm$ 0.04    | 0.18 $\pm$ 0.06    | <0.001  |
| MPV (fL)                       | 10.85 $\pm$ 1.16   | 11.32 $\pm$ 1.23   | 10.38 $\pm$ 0.86   | <0.001  |
| PDW (%)                        | 13.31 $\pm$ 2.75   | 14.64 $\pm$ 2.94   | 11.98 $\pm$ 1.73   | <0.001  |
| PRR                            | 10.01 $\pm$ 5.03   | 6.57 $\pm$ 2.44    | 13.43 $\pm$ 4.60   | <0.001  |
| PMR                            | 12.71 $\pm$ 6.90   | 8.11 $\pm$ 2.57    | 17.27 $\pm$ 6.84   | <0.001  |
| PHR                            | 1.09 $\pm$ 0.55    | 0.74 $\pm$ 0.21    | 1.43 $\pm$ 0.57    | <0.001  |
| Mortality (%)                  | 18.1               | 29.1               | 6.0                | <0.001  |

HB, hemoglobin; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; PHR, platelet to hemoglobin ratio; PLT, platelet; PMR, platelet to MPV ratio; PPR, platelet to PDW ratio; PRR, platelet to RDW ratio; RDW, red blood cell distribution width; WBC, white blood cell

Table 2. Multivariable logistic regression of in-hospital mortality for patients with type A acute aortic dissection

| Variables | OR    | 95% CI      | P-value |
|-----------|-------|-------------|---------|
| Age       | 0.931 | 0.905-0.979 | 0.003   |
| PPR       | 1.151 | 1.035-1.297 | 0.010   |

CI, confidence interval; OR, odds ratio; PPR, platelet to PDW ratio

2011]. These pro-inflammatory molecules facilitate the formation of PLT-neutrophilic complexes by enhancing neutrophilic rolling, adhesion, and recruitment. Both complexes and pro-inflammatory molecules could promote inflammation status and increase the severity of disease [Luo 2009]. In addition, intimal tearing of aortic dissection leads to exposure of subcutaneous components, leading to the release of tissue factors and triggering a coagulation cascade. In this process, a large amount of PLT is consumed. Research indicated the association between the high levels of PLT activation and the poor prognosis for aortic dissection, and a PLT  $\leq 119 \times 10^9/L$  was a strong predictor of an increased risk of hospitalization death for type A AAD patients, even in patients who are undergoing surgical intervention [Huang 2014]. This is consistent with our research results: The levels of PLT in the high-PPR group significantly surpass those in the low-PPR group. PDW is an indicator of the heterogeneity in platelet size, relating to the demand for platelets. PDW increases when there are both mature and

immature cells in the process of circulation. Increased PDW has been reported in coronary disorders and cerebral venous thrombosis [Kamislı 2013]. There also was a report that high PDW values have an association with more severe illness and had a higher risk of mortality [Zhang 2014]. Our study also showed that the levels of PDW were greatly higher in the low-PPR group.

In this study, mortality of the low-PPR group surpasses that of the high-PPR group ( $P < 0.001$ ). The AUC of PPR was 0.724 and was shown in the ROC curve. When 9.76 was selected as the best cut-off value of PPR, the sensitivity reached 56.4% and the specificity reached 80.6%. Patients with PPR  $< 9.76$  experienced a higher risk of in-hospital mortality than patients with PPR  $\geq 9.76$ . Therefore, PPR is a new parameter of platelets to better predict the mortality of post-operative patients with type A AAD. Furthermore, as a part of the complete blood count test, PPR is an easily obtained parameter by a blood cell analyzer at a low cost.

**Limitations:** Some limitations should be discussed. First,

our study was a single-center and retrospective cohort study with a relatively small sample. Further multi-center studies with larger sample sizes are needed to achieve a more detailed analysis. Second, some inflammatory and thrombotic biomarkers, such as CRP and D-dimer, could not be detected. Third, further research is needed to confirm the role of PPR.

## CONCLUSION

PPR is an independent predictor of in-hospital mortality for type A AAD postoperative patients. In addition, PPR is available in blood routines, which greatly reduces the financial burden on type A AAD patients.

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