

# Incidence, predictors, and prognosis of thrombocytopenia among patients undergoing intra-aortic balloon pumping in the intensive care unit: a propensity score analysis

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## ABSTRACT

**OBJECTIVE** To explore the incidence, predictors, and prognosis of intra-aortic balloon pumping (IABP)-related thrombocytopenia in critically ill patients.

**METHODS** This multi-center study used the eICU Collaborative Research Database V1.2, comprising data on > 130,000 patients from multiple intensive care units (ICUs) in America between 2014 and 2015. A total of 710 patients undergoing IABP were included. Thrombocytopenia was defined as a drop in platelet count > 50% from baseline. From the cohort, 167 patients who developed thrombocytopenia were matched 1:1 with 167 patients who did not, after propensity score (PS) matching. The associations between IABP-related thrombocytopenia and clinical outcomes were examined by multivariable logistic regression.

**RESULTS** Among 710 patients undergoing IABP, 249 patients (35.07%) developed thrombocytopenia. The APACHE IVa score was a predictor of thrombocytopenia [adjusted odds ratio (OR) = 1.09, 95% confidence interval (CI): 1.02–1.15]. After 1:1 PS matching, in-hospital mortality (adjusted OR = 0.76, 95% CI: 0.37–1.56) and in-ICU mortality (adjusted OR = 0.74, 95% CI: 0.34–1.63) were similar between the thrombocytopenia and non-thrombocytopenia groups. However, major bleeding occurred more frequently in the thrombocytopenia group (adjusted OR = 2.54, 95% CI: 1.54–4.17). In-hospital length of stay (LOS) and in-ICU LOS were significantly longer in patients who developed thrombocytopenia than in those who did not (9.71 vs. 7.36,  $P < 0.001$ ; 5.13 vs. 2.83,  $P < 0.001$ ).

**CONCLUSIONS** Among patients undergoing IABP in the ICUs, thrombocytopenia was not associated with a difference in in-hospital mortality or in-ICU mortality; however, thrombocytopenia was significantly associated with a greater risk of major bleeding and increased in-ICU and in-hospital LOS.

Intra-aortic balloon pump (IABP) is a commonly used circulatory assist device, which is positioned in the descending thoracic aorta to improve systemic hemodynamics.<sup>[1,2]</sup> Therefore, this device is routinely used in various clinical settings, such as high-risk percutaneous coronary intervention (PCI), acute myocardial infarction (MI), cardiogenic shock, and coronary artery bypass grafting (CABG).<sup>[3-7]</sup> However, IABP is reported to be associ-

ated with several complications, including hemorrhage, limb ischemia, embolization, and thrombocytopenia.<sup>[4,7,8]</sup>

The most frequent complication of IABP is thrombocytopenia, a drop in platelet count (DPC), which occurred in 43% to 82% of patients undergoing IABP.<sup>[9-11]</sup> The impact of IABP-related thrombocytopenia on clinical outcomes has remained unclear. Very few studies on IABP-related thrombocytopenia have

been performed, and they report conflicting results. In a prospective study of 252 patients treated by IABP, Roy, *et al.*<sup>[9]</sup> reported that thrombocytopenia was not a predictor of major bleeding or in-hospital death. Recently, Sheng, *et al.*<sup>[12]</sup> conducted another retrospective study of 222 patients with acute coronary syndrome (ACS); however, the results showed that IABP-related thrombocytopenia was correlated with increased in-hospital mortality, but not with thrombolysis in myocardial infarction bleeding or thromboembolic events. More importantly, these studies were single-center studies with a small number of subjects, which did not provide enough evidence to support their conclusions.

Therefore, we aimed to examine the incidence and prognostic impact on clinical outcomes of IABP-related thrombocytopenia in a multi-center large cohort of patients from a Collaborative Research Database. We further sought to explore the predictors of IABP-related thrombocytopenia.

## METHODS

### Study Database

This was a multi-center, retrospective study of patients from the eICU Collaborative Research Database (eICU-CRD) V1.2, which comprises data on 139,376 patients admitted to 335 intensive care units (ICUs) at 208 hospitals throughout America in 2014 and 2015.<sup>[13]</sup> The eICU-CRD V1.2 is made available and open to medical researchers online through the work of Philips Healthcare and Massachusetts Institute of Technology Laboratory for Computational Physiology.<sup>[14]</sup> The database contains details of patients, including vital signs, laboratory test results, medications, Acute Physiology and Chronic Health Evaluation (APACHE) score, admission-diagnosis, patient history, time-stamped diagnoses, treatments, and survival data on discharge.<sup>[13,15]</sup> Individual data have been previously deidentified. Access to the database was requested after registration, including completion of the required training course, agreement to instructions on data use, and application for access to the database project. The study design was approved by the Institutional Review Board of the Massachusetts Institute of Technology when data of all the patients were collected

from the database. The local Ethics Committee recommended that formal ethical approval was not required for this study.

### Study Population

The eICU-CRD V1.2 was searched to identify patients who underwent IABP after admission to the ICUs. Additionally, only the first IABP procedure was included in patients with multiple IABP procedures. The exclusion criteria were as follows: (1) age less than 18 years; (2) missing data on platelet counts; (3) platelet count  $< 100 \times 10^9/L$  before IABP; and (4) heparin-induced thrombocytopenia.

### Variable Definition

In the present study, we defined thrombocytopenia as a DPC  $> 50\%$  from the baseline platelet count. Baseline platelet count was the last value prior to initiation of IABP. Platelet counts were analyzed until the death of patients, discharge from the hospital, or nine days after IABP initiation. DPC was calculated using platelet count at baseline and the nadir after IABP initiation, with the following formula:  $(\text{baseline count} - \text{nadir count}) / \text{baseline count} \times 100\%$ . The APACHE IVa score is an established system of evaluating a patient's severity of illness on ICU admission, based on a group of patient-parameters including physiological measurements, comorbid burden, treatment, and admission-diagnosis.<sup>[15,16]</sup> "Prior thrombosis" was defined as patients with a history of venous thrombosis or pulmonary embolism. Cardiac diseases, including angina, MI, and cardiogenic shock, were defined when patients were recorded at the on-admission diagnosis or in-hospital diagnosis before IABP initiation. Details of percutaneous transluminal coronary angioplasty (PTCA) or CABG were recorded when the procedure was undertaken, based on the cardiac disease before IABP initiation. "Baseline laboratory values" were defined as the last laboratory test result values prior to IABP initiation. "Aggregation inhibitors" included the use of clopidogrel and ticlopidine. "Glycoprotein IIB/IIIA inhibitors" included the use of tirofiban, abciximab, or eptifibatide. "Thrombin inhibitors" included the use of argatroban and bivalirudin. "Thrombolytic therapy" was defined as the use of streptokinase or tenecteplase.

In regard to clinical outcomes, "Transfusion" was



a combination of red blood cell (RBC) and platelet transfusion of any number of units. “Thromboembolic event” included ischemic stroke, pulmonary embolism, deep vein thrombosis, and lower extremity arterial thromboembolism. “Post-procedural renal insufficiency” was defined as a rise in creatinine  $\geq 50\%$  from the baseline after IABP initiation. “Dialysis” was defined as hemodialysis or peritoneal dialysis. “Mechanical ventilation” was defined as patients requiring mechanical ventilation after the procedure. “Nadir and Maximum laboratory test results” values were the lowest and highest values, respectively, after IABP initiation.

### Clinical Outcomes

The primary clinical outcome was defined as in-hospital mortality. Secondary clinical outcomes included in-ICU mortality, major bleeding, in-hospital length of stay (LOS), and in-ICU LOS. “Major bleeding” was a composite variable consisting of hemorrhagic stroke, any clinically apparent bleeding with a decrease of  $\geq 30$  g/L from the baseline of hemoglobin concentration, one requiring transfusion of RBCs, or an acute loss of  $\geq 50$  g/L from the baseline of hemoglobin concentration over 72 h.

### Statistical Analysis

Quantitative variables were presented as median (interquartile range) and compared using the Mann-Whitney *U* test. Qualitative variables were presented as number and proportion and compared by means of the Pearson’s chi-square test or Fisher’s exact test. Multivariate logistic regression was performed to assess the association between thrombocytopenia and relevant clinical outcomes and identify the predictors of both thrombocytopenia and major bleeding. The calibration of the prediction models was determined by the Hosmer-Lemeshow goodness-of-fit test. A significant value of  $P < 0.05$  indicated a lack of fit. The model discrimination was assessed with the receiver operating characteristic curve. A model with an area under the curve (AUC) value  $> 0.7$  was considered as adequate discrimination. All tests were two-tailed and a value of  $P < 0.05$  was considered statistically significant.

A propensity score (PS) analysis was performed using a logistic regression model with thrombocyt-

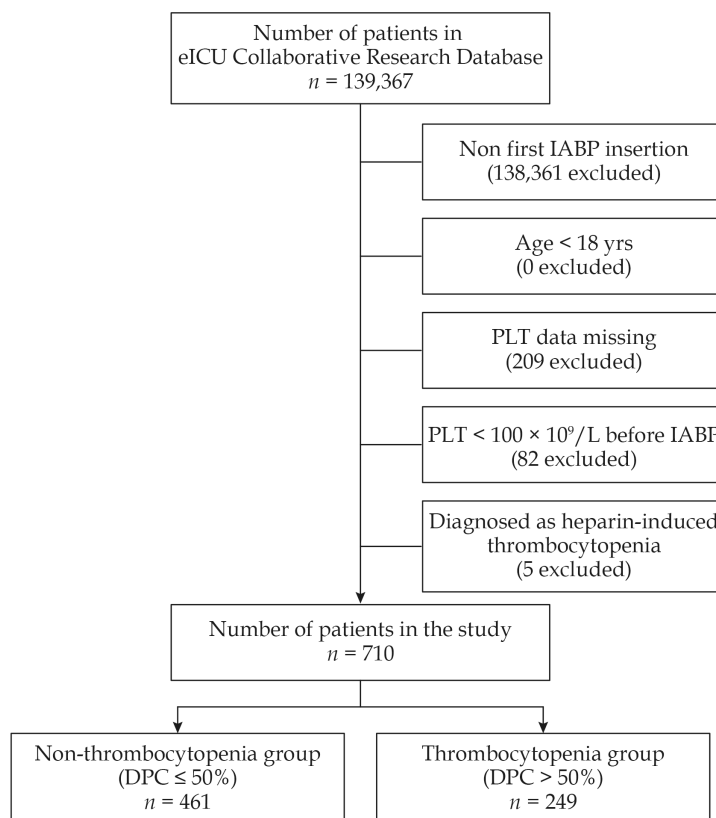
openia as the dependent variable and baseline characteristics as independent variables. Variables included in this model were age; sex; race (Caucasian); body mass index; APACHE IVa score; mean arterial pressure; history of hypertension, diabetes mellitus, hypercholesterolemia, and renal insufficiency; prior angina, MI, PCI, CABG, congestive heart failure (CHF), valve disease, stroke/transient ischemic attack, peripheral vascular disease, hemorrhage, and thrombosis; current angina, MI, PTCA, CABG, and cardiogenic shock; baseline values of platelets, hemoglobin, white blood cell (WBC), glucose, and creatinine; the use of aspirin, aggregation inhibitors, glycoprotein IIB/IIIA inhibitors, unfractionated heparin, low molecular weight heparin (LMWH), warfarin, fondaparinux, thrombin inhibitors, and thrombolytic therapy. A PS-matched cohort was created with a 1:1 ratio and nearest-neighbor match with a caliper of 0.02. The distributions of the PS before and after matching were also compared to further assess the degree of balance. Comparison of qualitative and quantitative variables between the matched cohorts was performed with McNemar’s test and the Mann-Whitney *U* test. All data were analyzed with IBM SPSS Statistics 23.0 (SPSS Inc., IBM, Armonk, NY, USA) and R Statistical Software 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

A total of 710 patients (Figure 1) were included in this study, of whom 249 patients (35.07%) developed thrombocytopenia with a DPC  $> 50\%$  from the baseline after IABP initiation. The median age was 66 years (25<sup>th</sup> to 75<sup>th</sup> percentile: 58–74 years), and 502 patients (70.70%) were male. The median APACHE IVa score of the study cohort was 56 (25<sup>th</sup> to 75<sup>th</sup> percentile: 40–82). Indications for IABP were support for PTCA (51.27%), support for CABG (17.89%), acute MI (6.62%), cardiogenic shock (2.81%), angina (3.38%), and other origins (18.03%).

### Baseline Characteristics

As detailed in Table 1, there were several differences in baseline characteristics between the two groups of the cohort. Women and those with high APACHE IVa scores were more likely to develop



**Figure 1** Flowchart of patient inclusion. DPC: drop in platelet count; IABP: intra-aortic balloon pumping; PLT: platelet.

thrombocytopenia. The baseline platelet count and glucose level were also high in the thrombocytopenia group; moreover, they more often reported the use of warfarin and fondaparinux. After the PS matching, 167 patients with thrombocytopenia were matched 1:1 with 167 patients without thrombocytopenia. Figure 2 shows the distribution of PS comparing the non-thrombocytopenia and thrombocytopenia groups before and after matching. In the matched cohort, there were no differences between the two groups for all variables including sex, APACHE IVa score, baseline platelet count, baseline glucose level, and the use of warfarin and fondaparinux (Table 1).

### Change in Platelet Counts

The platelet counts in the overall group began to decline after IABP initiation and continued to decrease through day 3 following the procedure (Figure 3). The median nadir platelet count was  $115 \times 10^9/L$  (25<sup>th</sup> to 75<sup>th</sup> percentile:  $82.00 \times 10^9/L$ – $155.25 \times 10^9/L$ ), resulting in a median DPC from baseline of 40.53% (25<sup>th</sup> to 75<sup>th</sup> percentile: 22.42%–55.70%). The

platelet counts then stabilized and returned to the baseline on day 7–8. The mean time of platelet counts decline to nadir was 4 days for patients with thrombocytopenia and 2–3 days for patients without thrombocytopenia. Moreover, the DPC was significantly higher in patients who developed thrombocytopenia than in those who did not (62.1% vs. 27.6%,  $P < 0.001$ ). The mean time taken for the platelet counts to return to the baseline was 9 days for patients with thrombocytopenia and 5 days for patients without thrombocytopenia.

### Clinical Outcomes in the Entire Population

As shown in Table 2, a significantly unadjusted difference in in-hospital mortality was observed in patients who developed thrombocytopenia compared with patients who did not (26.5% vs. 14.8%,  $P < 0.001$ ), with a similar difference seen in in-ICU mortality (22.1% vs. 11.9%,  $P < 0.001$ ). However, after adjustment for differences, thrombocytopenia was not an independent predictor of in-hospital mortality [odds ratio (OR) = 0.91, 95% confidence interval (CI): 0.49–1.70,  $P = 0.913$ ] or in-ICU mortality (OR =



0.98, 95% CI: 0.50–1.89,  $P = 0.940$ ]. The incidence of major bleeding increased with the development of thrombocytopenia, from 17.1% to 35.7% ( $P < 0.001$ ). Additionally, patients with thrombocytopenia still

remained at a significantly high risk for major bleeding (OR = 2.76, 95% CI: 1.80–4.23,  $P < 0.001$ ) on multivariate analysis. Both in-hospital LOS (10.81 vs. 8.09,  $P < 0.001$ ) and in-ICU LOS (5.13 vs. 2.92,  $P <$

**Table 1** Baseline characteristics before and after propensity score matching.

Variables	Entire cohort (n = 710)			Matched cohort (n = 334)		
	Non-thrombocytopenia (n = 461, DPC ≤ 50%)	Thrombocytopenia (n = 249, DPC > 50%)	P-value	Non-thrombocytopenia (n = 167, DPC ≤ 50%)	Thrombocytopenia (n = 167, DPC > 50%)	P-value
Age, yrs	65 (58–75)*	67 (59.5–74)*	0.235	66 (60–76)*	68 (60–74)*	0.827
Male	338 (73.3%)	164 (65.9%)	0.037	110 (65.9%)	111 (66.5%)	1.000
Caucasian	369 (80.0%)	187 (75.1%)	0.127	126 (75.4%)	130 (77.8%)	0.671
Body mass index, kg/m <sup>2</sup>	29.06 (25.16–33.01)*	27.95 (24.93–32.22)*	0.113	28.7 (24.95–33.27)*	27.66 (24.93–32.38)*	0.318
APACHE IVa score	52 (38.25–76)*	65 (43–98)*	< 0.001	60 (45–92)*	61 (42–93)*	0.544
Mean arterial pressure, mm Hg	76.33 (66.67–87.33)*	76.83 (65.58–90.33)*	0.724	76.33 (68–86.67)*	77.67 (65.67–90.33)*	0.679
Cardiovascular risk factors						
Hypertension	283 (61.4%)	161 (64.7%)	0.390	106 (63.5%)	106 (63.5%)	1.000
Diabetes mellitus	177 (38.4%)	85 (34.1%)	0.262	51 (30.5%)	52 (31.1%)	1.000
Hypercholesterolemia	52 (11.3%)	26 (10.4%)	0.733	20 (12.0%)	19 (11.4%)	1.000
Renal insufficiency	52 (11.3%)	27 (10.8%)	0.860	11 (6.6%)	14 (8.4%)	0.678
Cardiac history						
Prior angina	41 (8.9%)	18 (7.2%)	0.443	12 (7.2%)	13 (7.8%)	1.000
Prior myocardial infarction	100 (21.7%)	55 (22.1%)	0.903	41 (24.6%)	41 (24.6%)	1.000
Prior percutaneous coronary intervention	75 (16.3%)	41 (16.5%)	0.946	22 (13.2%)	26 (15.6%)	0.626
Prior coronary artery bypass grafting	34 (7.4%)	20 (8.0%)	0.753	8 (4.8%)	13 (7.8%)	0.359
Prior congestive heart failure	79 (17.1%)	45 (18.1%)	0.754	23 (13.8%)	28 (16.8%)	0.551
Prior valve disease	30 (6.5%)	25 (10.0%)	0.093	14 (8.4%)	18 (10.8%)	0.541
History of vascular diseases						
Prior stroke/Transient ischemic attack	31 (6.7%)	18 (7.2%)	0.800	7 (4.2%)	11 (6.6%)	0.481
Prior peripheral vascular disease	20 (4.3%)	13 (5.2%)	0.594	6 (3.6%)	8 (4.8%)	0.791
Prior hemorrhage	3 (0.7%)	2 (0.8%)	1.000	1 (0.6%)	1 (0.6%)	1.000
Prior thrombosis	20 (4.3%)	11 (4.4%)	0.961	7 (4.2%)	7 (4.2%)	1.000
In-hospital cardiac diseases						
Angina	45 (9.8%)	26 (10.4%)	0.773	21 (12.6%)	20 (12.0%)	1.000
Myocardial infarction	191 (41.4%)	89 (35.7%)	0.139	63 (37.7%)	66 (39.5%)	0.822
Percutaneous transluminal coronary angioplasty	234 (50.8%)	142 (57.0%)	0.110	92 (55.1%)	92 (55.1%)	1.000
Coronary artery bypass grafting	98 (21.3%)	41 (16.5%)	0.125	34 (20.4%)	31 (18.6%)	0.775
Cardiogenic shock	15 (3.3%)	5 (2.0%)	0.338	5 (3.0%)	3 (1.8%)	0.727





Continued

Variables	Entire cohort (n = 710)			Matched cohort (n = 334)		
	Non-thrombocytopenia (n = 461, DPC ≤ 50%)	Thrombocytopenia (n = 249, DPC > 50%)	P-value	Non-thrombocytopenia (n = 167, DPC ≤ 50%)	Thrombocytopenia (n = 167, DPC > 50%)	P-value
Laboratory values						
Baseline platelet, × 10 <sup>9</sup> /L	192 (147.25–237)*	216 (165.5–257)*	0.005	201(158–249)*	215 (165–254)*	0.978
Baseline hemoglobin, g/dL	12.40 (10.60–14.30)*	12.40 (10.70–14.30)*	0.767	12.3 (10.4–14.3)*	12.2 (10.2–14.5)*	0.862
Baseline white blood cells, × 10 <sup>9</sup> /L	12.00 (9.36–16.90)*	13.00 (9.20–18.42)*	0.202	12 (9.6–16.5)*	13.2 (9.5–18.4)*	0.583
Baseline glucose, mmol/L	8.06 (6.43–10.94)*	8.64 (6.50–12.92)*	0.037	8.39 (6.78–11.83)*	8.39 (6.5–11.28)*	0.739
Baseline creatinine, mg/dL	1.07 (0.87–1.35)*	1.12 (0.90–1.52)*	0.07	1.04 (0.84–1.27)*	1.08 (0.87–1.49)*	0.107
Periprocedural medication						
Aspirin	377 (81.8%)	199 (79.9%)	0.546	141 (84.4%)	132 (79.0%)	0.233
Aggregation inhibitors	168 (36.4%)	75 (30.1%)	0.090	58 (34.7%)	56 (33.5%)	0.913
Glycoprotein IIB/IIIA inhibitor	91 (19.7%)	37 (14.9%)	0.106	23 (13.8%)	23 (13.8%)	1.000
Unfractionated heparin	282 (61.2%)	151 (60.6%)	0.725	103 (61.7%)	106 (63.5%)	0.820
Low molecular weight heparin	95 (20.6%)	63 (25.3%)	0.151	42 (25.1%)	38 (22.8%)	0.683
Warfarin	45 (9.8%)	38 (15.3%)	0.030	20 (12.0%)	20 (12.0%)	1.000
Fondaparinux	1 (0.2%)	6 (2.4%)	0.015	1 (0.6%)	1 (0.6%)	1.000
Thrombin inhibitor	46 (10.0%)	31 (12.4%)	0.312	23 (13.8%)	15 (9.0%)	0.243
Thrombolytic therapy	3 (0.7%)	6 (2.4%)	0.099	1 (0.6%)	1 (0.6%)	1.000

Data are presented as n (%). \*Presented as median (interquartile range). APACHE: Acute Physiology and Chronic Health Evaluation; DPC: drop in platelet count.

0.001) were progressively lengthened in the thrombocytopenia group versus in the non-thrombocytopenia group.

Patients with thrombocytopenia were more likely to have other in-hospital complications, including transfusion, post-procedural renal insufficiency, dialysis, and mechanical ventilation (Table 2). However, there was no difference in thromboembolic events between the two groups (0.9% vs. 2.4%,  $P = 0.183$ ). After adjusting the differences, patients with thrombocytopenia remained at an increased risk for clinical complications, including transfusion (OR = 2.93, 95% CI: 1.51–5.68,  $P = 0.002$ ), post-procedural renal insufficiency (OR = 3.14, 95% CI: 2.03–4.88,  $P < 0.001$ ), dialysis (OR = 4.82, 95% CI: 2.02–11.46,  $P < 0.001$ ), and mechanical ventilation (OR = 1.83, 95% CI: 1.25–2.68,  $P = 0.002$ ).

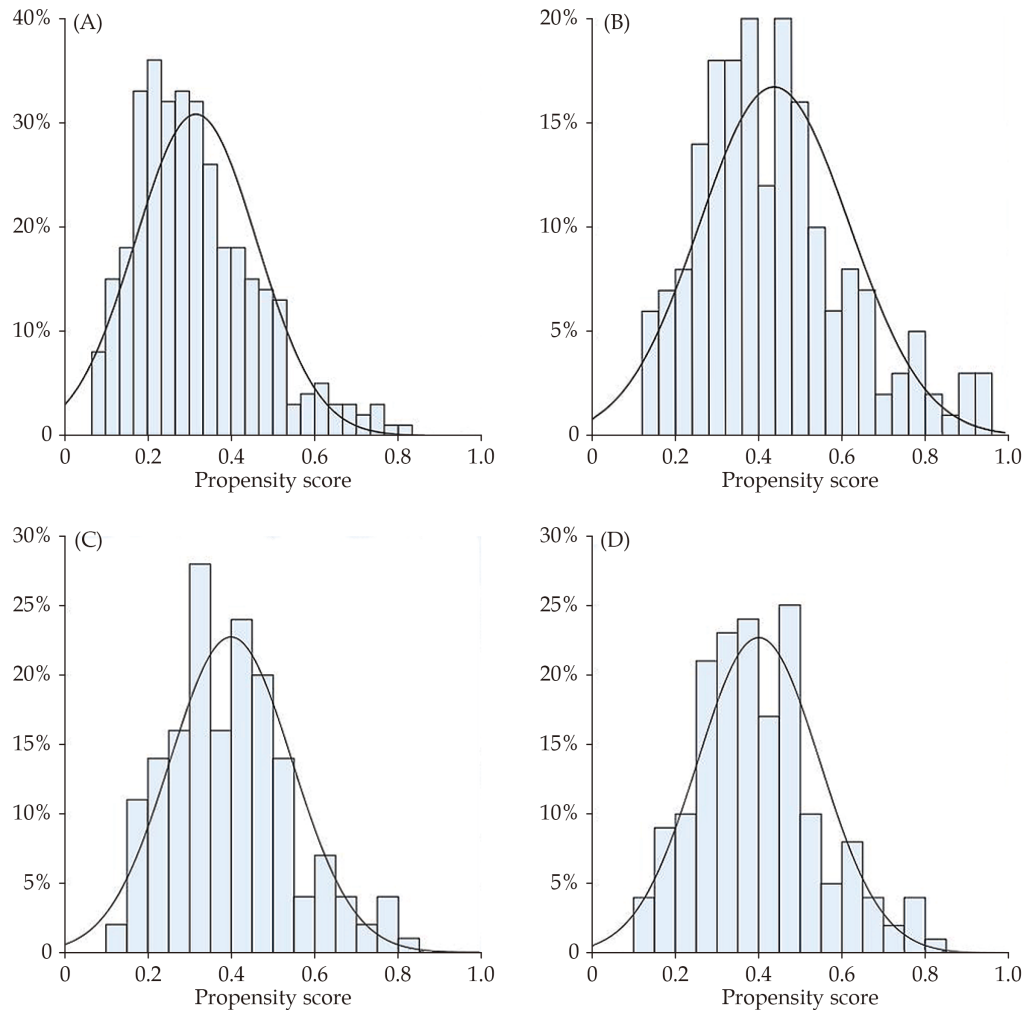
Greater severity of laboratory change could also be plotted among the thrombocytopenia group

(supplemental material, Table 1S). Patients who developed thrombocytopenia were more likely to have a lower nadir and a greater DPC ( $P < 0.001$ ), as well as hemoglobin level ( $P < 0.001$ ). The maximum values of WBC count ( $P < 0.001$ ) and creatinine level ( $P < 0.001$ ) were larger in the thrombocytopenia group than in the non-thrombocytopenia group, with a similarly larger increase in absolute value ( $P < 0.001$ ).

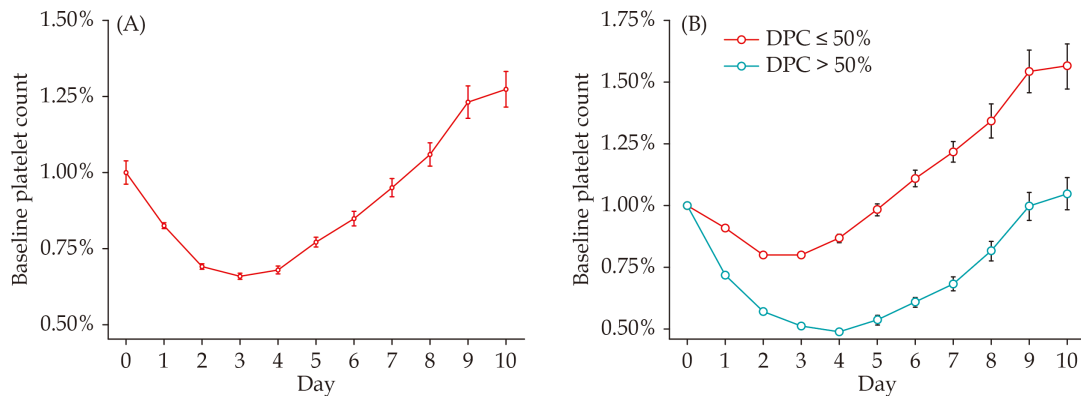
### Clinical Outcomes in the Propensity Score-matched Population

After the PS matching, no significant differences were seen between the two groups in in-hospital mortality (21.0% vs. 24.0%,  $P = 0.583$ ) or in-ICU mortality (18.6% vs. 21.0%,  $P = 0.671$ ) (Table 3). The incidence rate of major bleeding was higher in the thrombocytopenia group than in the non-thrombocytopenia group (39.5% vs. 22.2%,  $P = 0.001$ ). Similar





**Figure 2** Distribution plot of propensity score comparing non-thrombocytopenia group and thrombocytopenia group before (A & B) and after (C & D) matching.



**Figure 3** Changing curve of platelet count. (A): Platelet count as a percentage of baseline  $\pm$  standard error; and (B): platelet count as a percentage of baseline  $\pm$  standard error according to DPC. DPC: drop in platelet count.

results remained in in-hospital mortality (OR = 0.76, 95% CI: 0.37–1.56,  $P = 0.448$ ), in-ICU mortality (OR = 0.74, 95% CI: 0.34–1.63,  $P = 0.459$ ), and major

bleeding (OR = 2.54, 95% CI: 1.54–4.17,  $P < 0.001$ ) after multivariate analysis. Moreover, patients with thrombocytopenia were still more likely to stay

**Table 2 In-hospital clinical outcomes in the entire population.**

	Non-thrombocytopenia (n = 461, DPC ≤ 50%)	Thrombocytopenia (n = 249, DPC > 50%)	P-value	Unadjusted OR	95% CI	Adjusted OR	95% CI	P-value
Clinical outcomes								
In-hospital mortality	68 (14.8%)	66 (26.5%)	< 0.001	2.08	1.42–3.05	0.91	0.49–1.70	0.913
In-ICU mortality	55 (11.9%)	55 (22.1%)	< 0.001	2.08	1.38–3.13	0.98	0.50–1.89	0.940
Major bleeding	79 (17.1%)	89 (35.7%)	< 0.001	2.69	1.89–3.84	2.76	1.80–4.23	< 0.001
Hospital LOS, day	8.09 (4.86–15.42)*	10.81 (6.64–19.41)*	< 0.001	–	–	–	–	–
ICU LOS, day	2.92 (1.79–5.19)†	5.13 (2.92–9.69)†	< 0.001	–	–	–	–	–
Other clinical complications								
Transfusion	28 (6.1%)	39 (15.7%)	< 0.001	2.87	1.72–4.80	2.93	1.51–5.68	0.002
Transfusion of red blood cell	27 (5.9%)	38 (15.3%)	< 0.001	2.90	1.72–4.87	2.89	1.47–5.69	0.002
Transfusion of platelet	8 (1.7%)	9 (3.6%)	0.118	2.12	0.81–5.57	–	–	–
Tromboembolic events	4 (0.9%)	6 (2.4%)	0.183	2.82	0.79–10.09	–	–	–
Post-procedural renal insufficiency	70 (15.2%)	87 (34.9%)	< 0.001	2.97	2.05–4.29	3.14	2.03–4.88	< 0.001
Dialysis	16 (3.5%)	35 (14.1%)	< 0.001	4.55	2.46–8.40	4.82	2.02–11.46	< 0.001
Mechanical ventilation	172 (37.3%)	143 (57.4%)	< 0.001	2.27	1.66–3.10	1.83	1.25–2.68	0.002

Data are presented as n (%). \*Presented as median (interquartile range). CI: confidence interval; DPC: drop in platelet count; ICU: intensive care unit; LOS: length of stay; OR: odds ratio.

**Table 3 In-hospital clinical outcomes in the propensity score-matched cohort.**

	Non-thrombocytopenia (n = 167, DPC ≤ 50%)	Thrombocytopenia (n = 167, DPC > 50%)	P-value	Adjusted OR	95% CI	P-value
Clinical outcomes						
In-hospital mortality	35 (21.0%)	40 (24.0%)	0.583	0.76	0.37–1.56	0.448
In-ICU mortality	31 (18.6%)	35 (21.0%)	0.671	0.74	0.34–1.63	0.459
Major bleeding	37 (22.2%)	66 (39.5%)	0.001	2.54	1.54–4.17	< 0.001
Hospital LOS, day	7.36 (3.77–10.42)*	9.71 (6.36–16.81)*	< 0.001	–	–	–
ICU LOS, day	2.83 (1.63–4.88)*	5.13 (2.96–9.67)*	< 0.001	–	–	–
Other clinical complications						
Transfusion	15 (9.0%)	26 (15.6%)	0.091	2.22	1.05–4.70	0.036
Transfusion of red blood cell	15 (9.0%)	25 (15.0%)	0.123	2.01	0.96–4.24	0.066
Transfusion of platelet	4 (2.4%)	6 (3.6%)	0.688	–	–	–
Tromboembolic events	2 (1.2%)	2 (1.2%)	1.000	–	–	–
Post-procedural renal insufficiency	27 (16.2%)	57 (34.1%)	0.001	3.04	1.76–5.27	< 0.001
Dialysis	5 (3.0%)	21 (12.6%)	0.002	7.58	2.18–26.30	0.001
Mechanical ventilation	70 (41.9%)	92 (55.1%)	0.020	1.89	1.19–2.98	0.007

Data are presented as n (%). \*Presented as median (interquartile range). CI: confidence interval; DPC: drop in platelet count; ICU: intensive care unit; LOS: length of stay; OR: odds ratio.

longer both in-hospital (9.71 vs. 7.36,  $P < 0.001$ ) and in-ICU (5.13 vs. 2.83,  $P < 0.001$ ).

Patients with thrombocytopenia reported a high incidence of post-procedural renal insufficiency, dialysis, and mechanical ventilation; however, the frequency of transfusion (9.0% vs. 15.6%,  $P = 0.091$ )

and thromboembolic events (1.2% vs. 1.2%,  $P = 1.000$ ) was similar (Table 3). However, significant adjusted differences were maintained in clinical complications, including transfusion (OR = 2.22, 95% CI: 1.05–4.70,  $P = 0.036$ ), post-procedural renal insufficiency (OR = 3.04, 95% CI: 1.76–5.27,  $P <$





0.001), dialysis (OR = 7.58, 95% CI: 2.18–26.30,  $P = 0.001$ ), and mechanical ventilation (OR = 1.89, 95% CI: 1.19–2.98,  $P = 0.007$ ).

In the PS-matched cohort, laboratory change was similar to the result observed in the entire cohort (supplemental material, Table 2S). The thrombocytopenia group also had a greater likelihood of a lower nadir and a greater DPC ( $P < 0.001$ ), as well as hemoglobin ( $P < 0.001$ ). Similarly, the WBC ( $P = 0.002$ ) and creatinine ( $P < 0.001$ ) maximum value was larger in the thrombocytopenia group, with a larger increase in absolute value ( $P < 0.001$ ).

### Predictors of IABP-related Thrombocytopenia

Table 4 indicates that baseline platelet count, baseline glucose level, diabetes mellitus, prior valve diseases, in-hospital PTCA, and the use of glycoprotein IIB/IIIA inhibitors were independent predictors of IABP-related thrombocytopenia. Another predictor worthy of notice was APACHE IVa score (OR = 1.09, 95% CI: 1.02–1.15,  $P = 0.01$ ), suggesting that patients with more severe illness on ICU admission had high risks of acquiring IABP-related thrombocytopenia. Sex, although significantly associated univariate, did not remain a risk factor after multiple adjustment. The prediction model demonstrated adequate calibration and discriminatory capacity for the patients as a whole (Hosmer-Lemeshow goodness-of-fit test  $P = 0.758$ , AUC = 0.648, 95% CI: 0.603–0.694).

### Predictors of Major Bleeding

The predictors of major bleeding in the entire cohort were listed (supplemental material, Table 3S).

**Table 4** Independent predictive factors of thrombocytopenia (platelet count drop > 50%).

Variable	Odds ratio	95% CI	P-value
APACHE IVa score (per 10-unit increase)	1.09	1.02–1.15	0.01
Baseline platelet count (per 10-unit increase)	1.03	1.00–1.05	0.06
Baseline glucose	1.04	1.00–1.09	0.08
Diabetes mellitus	0.64	0.43–0.97	0.03
Prior valve diseases	2.07	1.06–4.07	0.03
In-hospital percutaneous transluminal coronary angioplasty	1.43	0.96–2.13	0.08
Glycoprotein IIB/IIIA inhibitor	0.54	0.32–0.91	0.02

APACHE: Acute Physiology and Chronic Health Evaluation.

Beyond thrombocytopenia, other variables including APACHE IVa score, baseline platelet count, baseline glucose, hypercholesterolemia, prior angina, prior CHF, prior valve diseases and LMWH use were predictive factors of major bleeding. Notably, despite close univariate association of in-hospital CABG with major bleeding (unadjusted OR = 1.67, 95% CI: 1.11–2.51,  $P = 0.013$ ), surgery did not remain a risk factor after multiple adjustment. Furthermore, adequate calibration and discriminatory capacity were observed in this model for the overall patients (Hosmer-Lemeshow goodness-of-fit test  $P = 0.219$ , AUC = 0.710, 95% CI: 0.665–0.755).

## DISCUSSION

The current study revealed the incidence, predictors, and prognosis of thrombocytopenia in a large retrospective, multi-center, cohort of patients undergoing IABP in the ICUs. Thrombocytopenia occurred among 35.07% of patients undergoing IABP in the entire cohort. APACHE IVa score was found to be a significant predictor of both IABP-related thrombocytopenia and major bleeding. No association between IABP-related thrombocytopenia and in-hospital or in-ICU mortality was observed, both in the entire cohort and the PS-matching cohort. However, IABP-related thrombocytopenia was significantly associated with a longer duration of ICU and hospital LOS, and a greater risk of major bleeding and other clinical complications.

Incidence of thrombocytopenia varied between different studies with various definitions of thrombocytopenia.<sup>[9,12,17–19]</sup> In a study by Sheng, *et al.*,<sup>[12]</sup> thrombocytopenia, defined as a nadir platelet count of  $< 150 \times 10^9/L$  or DPC > 50%, was observed in 54.5% of enrolled patients undergoing IABP with ACS. A similar definition yielded the incidence of 43.3% among patients undergoing IABP in the coronary care unit.<sup>[9]</sup> Among patients treated with PCI, the incidence of thrombocytopenia was 16.2%; however, in this study, thrombocytopenia was only defined as DPC  $\geq 25\%$ .<sup>[18]</sup> In a study of ACS patients by Wang, *et al.*,<sup>[19]</sup> 12.5% patients were reported to develop in-hospital thrombocytopenia (nadir platelet  $< 150 \times 10^9/L$ ) after treatment with ACS therapies. Therefore, the studies related to thrombocytopenia still lack a uniform definition of post-procedure

thrombocytopenia. In our study, despite the exclusion of patients with baseline platelet count  $< 100 \times 10^9/L$  from the study cohort, 163 patients (22.96% among the entire cohort) had marginally low baseline platelet count ( $100 \times 10^9/L$ – $150 \times 10^9/L$ ). In such patients, the definition of IABP-related thrombocytopenia, if based on nadir of platelet count post-IABP, might be met despite a minor effect of the IABP on the platelet count. We intended to focus on the impact of IABP-related DPC rather than absolute count value on clinical outcomes. Therefore, thrombocytopenia was defined as a DPC  $> 50\%$  from the baseline platelet count. We found that the incidence of thrombocytopenia was 35.09%, slightly lower to that observed in previous IABP-related studies.

Several prior reports have indicated that the impact of IABP-related thrombocytopenia on clinical outcomes remains uncertain.<sup>[9,12]</sup> In this study, the entire cohort had lower platelet counts at the baseline and nadir compared to previous studies.<sup>[9,12]</sup> More importantly, the platelet count drop was higher. Major bleeding (23.7%) occurred far more frequently compared with the study results of Roy, *et al.*<sup>[9]</sup> (8.3%) and Sheng, *et al.*<sup>[12]</sup> (5.4%). The incidence of in-hospital mortality (18.9%) was higher than that reported by Sheng, *et al.*<sup>[12]</sup> (5.9%), but slightly lower than that reported by Roy, *et al.*<sup>[9]</sup> (21.4%). Our work showed that IABP-related thrombocytopenia was not significantly associated with in-hospital or in-ICU mortality in the critically ill patients. Among the entire population however, on univariate analysis, patients with thrombocytopenia had a greater risk of in-hospital death (26.5% vs. 14.8%,  $P < 0.001$ ) and in-ICU death (22.1% vs. 11.9%,  $P < 0.001$ ) than those who did not. That might be related to the higher APACHE IVa score among the thrombocytopenia group, which revealed that this group of patients presented with a more severe illness on admission to ICU and higher possibility of worsening outcomes. After controlling for patient differences, IABP-related thrombocytopenia was not a predictor of in-hospital or in-ICU mortality.

Despite the negative finding of in-hospital and in-ICU mortality, IABP-related thrombocytopenia was significantly associated with major bleeding. This finding was different from two previous studies, which both reported that thrombocytopenia was

not a predictor of major bleeding.<sup>[9,12]</sup> Moreover, IABP-related thrombocytopenia was also associated with other clinical complications, including transfusion, post-procedural renal insufficiency, dialysis, and mechanical ventilation. Additionally, patients with thrombocytopenia were more likely to stay longer in the ICU and hospital. This might be because the greater incidence of clinical complications contributed to the longer duration of ICU and hospital LOS. These findings have never been reported by previous studies. Taken together, these findings suggested that IABP-related thrombocytopenia was not a fatal clinical problem but might worsen the severity of patient illness and prolong the ICU and hospital LOS.

The current study showed that patients who developed thrombocytopenia presented with a higher APACHE IVa score, use of glycoprotein IIB/IIIA inhibitor, and history of diabetes mellitus and valve diseases. Previous studies reported that thrombocytopenia was correlated with older age; female sex; weight; renal insufficiency; duration of IABP; and several medications, including heparin, clopidogrel, and glycoprotein IIB/IIIA inhibitors.<sup>[20–23]</sup> Thrombocytopenia among patients undergoing IABP can be the consequence of different causes. It may be either an immune reaction due to heparins or glycoprotein IIB/IIIA inhibitors,<sup>[24,25]</sup> a loss of consumption due to PCI or IABP, acute heart failure, sepsis, renal failure, or multiple organ dysfunction.<sup>[23,26–28]</sup> Our study notably reported the association of APACHE IVa score with the development of thrombocytopenia. The APACHE IVa score is an evaluation system to present illness severity of patients on admission to the ICU. Patients with high APACHE IVa scores might have severe sepsis, organ failure, and even multiple organ dysfunction. In such patients, the DPC might be caused by these factors. Therefore, APACHE IVa score was the significant predictor of IABP-related thrombocytopenia.

## STRENGTHS AND LIMITATIONS

This study had several strengths. Firstly, this study was based on a large, retrospective, multi-center compared to previous single-center studies on IABP. Secondly, the APACHE IVa score was used as a quantitative variable and was included as one of the covariates in the multivariate logistic regres-



sion. However, there were also several limitations that require consideration. Firstly, although a multivariate analysis and a PS analysis were used to adjust for differences in baseline characteristics, the potential for unaccounted confounding factors might still be present in this study. Secondly, only the DPC was taken into consideration, so the impact of platelet count nadir on the clinical outcomes was not explored in this study. Therefore, the risks of clinical outcomes might be overestimated among patients with DPC  $\leq 50\%$ , but not platelet count nadir  $< 150 \times 10^9/L$ . Thirdly, IABP duration, which was reported to be related to thrombocytopenia and major bleeding among patients undergoing IABP,<sup>[9,12]</sup> was not available in the eICU-CRD V1.2 online. Therefore, it was not included as a variable in the study, and we cannot ignore the possibility of its significance. Last but not least, we only studied the data of in-hospital outcomes. Further research is required to confirm the long-term outcomes, which might provide more powerful information on clinical decisions.

## CONCLUSIONS

In conclusion, thrombocytopenia occurred among 35.07% of patients who underwent IABP in ICUs. It was not associated with a difference in in-hospital mortality or in-ICU mortality, but significantly associated with a greater risk of increased in-ICU LOS, in-hospital LOS, major bleeding, and other clinical complications. APACHE IVa score was a potential predictor of IABP-related thrombocytopenia.

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