Baseline Platelet Count Predicts Infarct Size and Mortality after Acute Myocardial Infarction

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Abstract

Introduction Platelets greatly contribute to cardiovascular diseases. We sought to explore the association of platelet counts with infarct size and outcome in patients presenting with acute ST-segment elevation MI (STEMI) treated with primary percutaneous coronary intervention (PPCI).

Methods and Results In this retrospective study, we grouped 1,198 STEMI patients into tertiles (T) based on platelet count on admission: T1 = 102–206 [10^9 platelets/L] ($n = 402$), T2 = 207–259 [10^9 platelets/L] ($n = 396$), and T3 = 260–921 [10^9 platelets/L] ($n = 400$). Primary endpoint was 1-year all-cause mortality. Patients with highest platelet counts on admission showed the greatest area at risk and infarct size: area at risk (median) was 22.0% (interquartile range [IQR]: 12.0–39.8%) in T1, 21.0% (IQR: 11.0–37.1%) in T2, and 26.0% (IQR: 14.9–45.0%) of the left ventricle in T3 ($p = 0.003$); final infarct sizes after 7 to 14 days were as follows: 10.0% (IQR: 2.0–21.0%) in T1, 9.0% (IQR: 2.0–20.7%) in T2, and 12.0% (IQR: 3.0–27.3%) of the left ventricle in T3 ($p = 0.015$) as serial imaging revealed. At 1 year, 16 all-cause deaths occurred in T1, 5 in T2, and 22 in T3 (log-rank test, $p = 0.006$). After adjustment, T1 and T3 were associated with all-cause 1-year mortality (T1: hazard ratio [HR] = 3.40, 95% confidence interval [CI] = 1.23–9.54, $p = 0.02$; T3: HR = 3.55, 95% CI = 1.23–9.78, $p = 0.01$) compared with T2. At 5 years, all-cause mortality remained numerically higher in the T1 and T3.

Conclusions In patients with STEMI undergoing PPCI, low and high blood platelet levels on admission were associated with increased long-term mortality (►Fig. 1).

Keywords
- platelets
- myocardial infarction
- SPECT imaging
- infarct size
- outcome

Introduction

Platelets are anucleate blood cells which are primarily produced in the bone marrow in a process called thrombopoiesis. They derive from megakaryocytes through thrombopoietin–thrombopoietin receptor interactions which induce the formation of pro-platelets.[1] Platelets are implicated in hemostasis and arterial thrombosis and hence significantly contribute to development and exacerbation of cardiovascular disease. In that light, acute myocardial infarction (MI) is characterized by erosion or rupture of atherosclerotic plaques inside coronary arteries leading to

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thrombus formation (atherothrombosis) which may result in obstruction of blood flow and subsequent ischemia of downstream located tissue.[2–4] As a consequence, targeting platelet activity is a cornerstone in acute coronary syndrome (ACS)/MI treatment.[5] Apart from promoting only thrombus formation, platelets can trigger acute coronary events also by interacting with leukocytes, endothelial cells, and the coagulation system resulting in thromboinflammation.[1,6]

While a higher platelet count on presentation was found to be associated with adverse clinical outcomes,[7–11] studies that specifically examined the impact of platelet counts on myocardial ischemia and recovery together with outcome in patients with acute ST-segment elevation myocardial infarction (STEMI) are scarce. Therefore, we here explore the association of platelet counts with infarct size using serial single-photon emission computed tomography (SPECT) imaging and long-term mortality in patients with STEMI undergoing primary percutaneous coronary intervention (PPCI).

Methods

Study Design

Details of the study patients were described earlier.[12–14] By design, the study represents a retrospective analysis. In brief, between January 2002 and December 2007, patients with STEMI undergoing PPCI and serial scintigraphic imaging at two tertiary cardiac care centers (Deutsches Herzzentrum Muünchen and Klinikum rechts der Isar, both Technical University of Munich, Munich, Germany) were included in this study. The diagnosis of STEMI was based on chest pain lasting $\geq$20 minutes and persistent ST-segment elevation $\geq$1 mm in at least two extremities or $\geq$2 mm in at least two chest leads or new onset of left bundle branch block. As reported recently,[13] 200 out of 1,406 STEMI patients were excluded because the time-of-day at symptom onset was not clearly documented. Hence, the remaining cohort of 1,206 patients was included into this analysis with additional information (e.g., symptom onset) for further analysis.[12] Two patients were excluded because admission platelet measurements were not available. To exclude patients with severe thrombocytopenia, six patients with platelet counts below 100 [10^9/L] on admission were excluded. Finally, 1,198 STEMI patients with serial scintigraphic data were included in this study. All patients gave written informed consent for PPCI and imaging procedures. The study protocol was approved by the institutional ethics committee (454/21 S-KH) and conforms to the Declaration of Helsinki.

Angiography and PPCI

The culprit lesion in the infarct-related artery was identified during coronary angiography by the presence of acute occlusion, intraluminal filling defects (or thrombus), ulcerated plaques with contrast-filled pockets protruding into the plaque with or without delayed contrast wash-out, extraluminal contrast, dissection, or intraluminal flaps. Coronary artery disease in non-culprit lesions was defined as coronary stenosis of $\geq$50% lumen obstruction.[13] Left ventricular ejection fraction (LV-EF) on admission (baseline) and after 6 months was measured on left ventricular angiograms using the area-length method.[13] Unfractionated heparin was used for periprocedural anticoagulation.[13] The antithrombotic regime included clopidogrel, a loading dose of 600 mg, and aspirin 325 to 500 mg.[13] Chronic antithrombotic therapy consisted of clopidogrel, 150 mg until discharge (no more than 3 days) mostly followed by 75 mg/day for $\geq$1 month and aspirin 200 mg/day indefinitely.[13] Few patients were treated with ticlopidine (250 mg twice/day) instead of clopidogrel and aspirin 200 mg/day indefinitely. If indicated—mostly due to new onset of atrial fibrillation—patients were treated with phenprocoumon in combination with either aspirin and clopidogrel or aspirin and ticlopidine, respectively.[12]

Measurement of Myocardial Area at Risk and Final Infarct Size Using SPECT

99mTc-sestamibi SPECT imaging studies were performed as described previously.[12–14] In brief, SPECT imaging was performed twice in each patient at predefined time points using the following protocol: *First measurement*: 99mTc-sestamibi (27 mCi [1,000 MBq]) was injected intravenously before PPCI and imaging was performed 6 to 8 hours afterward to assess the perfusion defect. This estimates the myocardial area at risk. *Second measurement*: 99mTc-sestamibi was injected intravenously 7 to 14 days after PPCI and imaging was performed 6 to 8 hours afterward. This estimates the final infarct size. Perfusion defects were defined as $<$50% uptake of 99mTc-sestamibi and were expressed as percentage of the left ventricle.[12–14] Myocardial salvage index (i.e., relative salvage) was calculated as initial myocardial area at risk minus final infarct size divided by initial myocardial area at risk.[12,13] The myocardial salvage index represents the proportion of initial myocardial area at risk salvaged by reperfusion therapy. All measurements were performed by investigators who were not aware of the clinical or angiographic data.[12–14]

Laboratory Data, Medical History, and Definitions

Laboratory measurements were performed daily at the institute of laboratory medicine of our hospital and extracted from patients' charts up to 10 days of hospitalization. Baseline platelet count refers to the first available measurement of platelet count recorded on admission. For the purpose of this analysis, patients were divided into three groups according to the tertiles of platelet count on admission: a group with platelet count in the 1st tertile (T1 group), a group with platelet count in the 2nd tertile (T2 group), and a group with platelet count in the 3rd tertile (T3 group). Normal platelet count was defined as 140 to 400 [10^9/L]. Creatine kinase myocardial band (CK-MB) was measured daily and peak levels were defined as the highest value obtained during hospitalization. CK-MB was considered an enzymatic estimate of infarct size. Renal function was assessed by calculating the creatinine clearance according to the Cockroft–Gault formula.

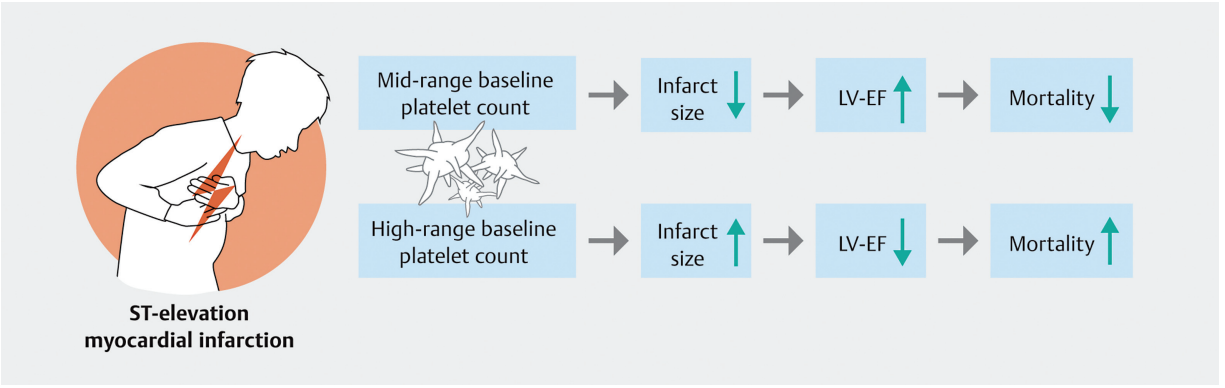

Fig. 1 In patients with ST-elevation myocardial infarction, high-range blood platelet counts on admission are associated with larger infarct size and reduced left ventricular (LV)-function. Both low- and high-range blood platelet counts on admission are associated with long-term mortality compared to patients with mid-range platelet counts.

Study Outcomes and Follow-up

The primary endpoint was 1-year all-cause mortality. Secondary endpoints were: myocardial salvage index, LV-EF (at 6 months), non-fatal MI (at 1- and 5-year follow-up), 5-year all-cause mortality, and MACE (1- and 5-year follow-up). As a standard practice in our institutions at the time of patient's recruitment, a repeat coronary angiography at 6 months after the index procedure was scheduled. The 6-month angiograms were used for the assessment of the LV-EF at this time point. Nonfatal MI was diagnosed based on the development of new abnormal Q waves in two or more contiguous chest or two or more adjacent extremity leads, or an elevation of CK-MB more than two times (more than three times for 48 hours after a percutaneous coronary intervention [PCI] procedure) the upper limit of normal in the presence of ischemia symptoms.[13] Follow-up information was obtained by staff members who were not aware of the clinical data via phone calls 30 days after PCI, 1 year after PCI, and yearly thereafter.[12,13] Data on mortality were obtained from hospital records, death certificates, or phone contact with patients' relatives or referring physicians.[12,13]

Statistical Analysis

Continuous data are shown as mean ± standard deviation or median with 25th to 75th percentiles and 10th to 90th percentiles depending on the distribution of normality and compared with one-way ANOVA, Kruskal–Wallis test (plus Dunn's multiple comparisons test).[12,13] Discrete variables were shown as proportions (percentages) and compared with chi-square test.[12,13] Long-term clinical outcomes were assessed using the Kaplan–Meier method and log-rank test. Multivariable Cox proportional hazards model was used to assess the association between baseline platelet count and both all-cause mortality and MACE as described previously.[12] Hazard ratios (HRs) were shown with 95% confidence intervals (CIs). Age, heart rate (on admission), systolic blood pressure (on admission), creatinine clearance, sex, type II diabetes, Killip class on admission, previous MI, number of diseased vessels, platelet counts on admission were entered into the model. In the second model, leukocyte count and CRP level on admission or on day 1 were added alongside other baseline variables. A two-sided p-value of <0.05 was considered to indicate statistical significance. IBM SPSS Statistics version 29 and GraphPad Prism 9 were used for statistical analysis and visualization of data.

Results

Baseline Data

This study included 1,198 patients who were categorized in groups according to the tertiles of platelet count: a group with platelet count in the 1st tertile (T1 group; platelet count, 102–206 [10^9/L]; $n = 402$), a group with platelet count in the 2nd tertile (T2 group; platelet count, 207–259 [109/L]; $n = 396$), and a group with platelet count in the 3rd tertile (T3 group; platelet count, 260–921 [10^9/L]; $n = 400$). Median platelet counts on admission were 183 [10^9/L] in the T1 group, 232 [10^9/L] in the T2 group, and 294 [10^9/L] in the T3 group (►**Fig. 2A**). Platelet count change over the hospital course is shown in ►**Supplementary Fig. S1A** (available in the online version only) for all patients and in ►**Supplementary Fig. S1B** (available in the online version only) for individual groups. Baseline characteristics of patients in groups T1 to T3 are shown in ►**Table 1**. The baseline variables differed between the groups with respect to age, sex, current smoking, family history for coronary artery disease (CAD), creatinine clearance on admission, previous coronary artery bypass graft surgery (CABG), and location of the culprit lesion. Data on medication on admission and at discharge are included in ►**Supplementary Table S1** (available in the online version only). Ninety-two patients in T1 (22.9%), 70 patients in T2 (17.7%), and 58 patients in T3 (14.5%) were on aspirin; 4 patients in T1 (1.0%), 4 patients in T2 (1.0%), and 3 patients in T3 (0.8%) were on clopidogrel; and 4 patients in T1 (1.0%), 3 patients in T2 (0.8%), and 2 patients in T3 (0.5%) were on both drugs on admission. Most patients received aspirin and clopidogrel after PPCI, since other potent P2Y12 inhibitors were not available at the time when the study was conducted. The antiplatelet treatment did not differ on admission or at discharge between the three groups. All patients were advised to take clopidogrel for 12 months and to continue aspirin indefinitely after the index event.

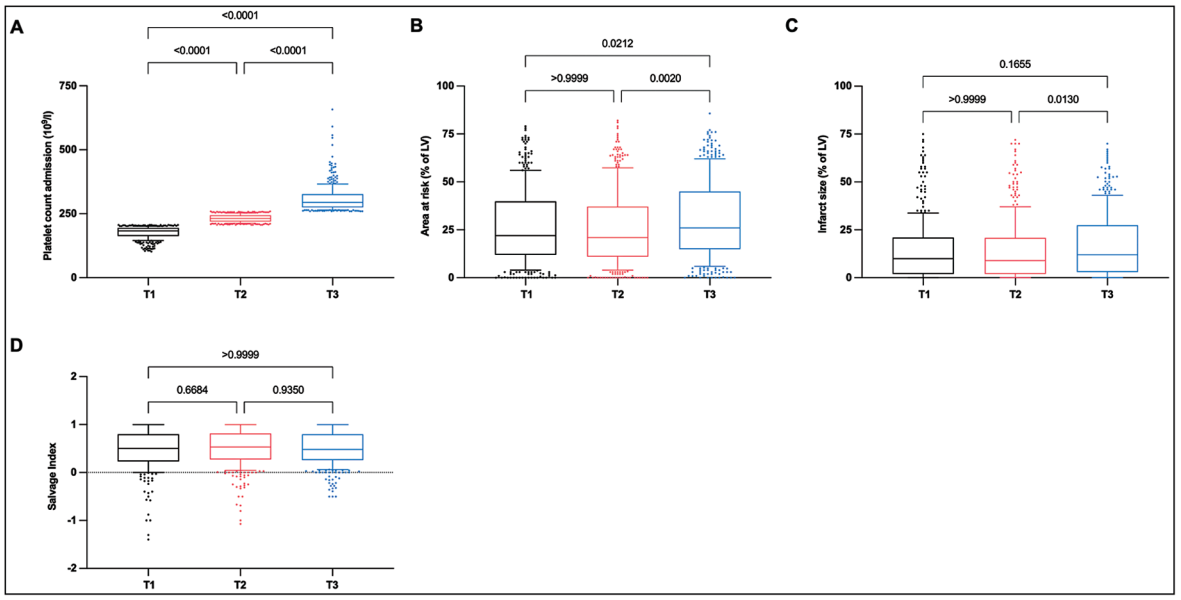

Fig. 2 (**A**) Platelet counts on admission (tertile-based analysis). (**B**) Initial myocardial area at risk (% of the left ventricle) assessed by first scintigraphic imaging prior to primary percutaneous coronary intervention (PPCI). (**C**) Final infarct size assessed by second scintigraphic imaging 7–14 days after PPCI (% of the left ventricle). (**D**) Myocardial salvage index in different tertiles of platelet count on admission. Data are median with 25th–75th percentiles (boxes), 10th–90th percentiles (bars), and values outside the given percentiles (dots). LV, left ventricle; T1, tertile 1; T2, tertile 2; T3, tertile 3.

Baseline Platelet Counts and Infarct Size

Data on scintigraphic- and blood-based measures of infarct sizes are presented in ►**Fig. 2B–D** and ►**Supplementary Fig. S2A, B** (available in the online version only). Myocardial area at risk or initial perfusion defect before PPCI (median) was 22.0% (interquartile range [IQR]: 12.0–39.8%), 21.0% (IQR: 11.0–37.1%), and 26.0% of the left ventricle (IQR: 14.9–45.0%) in T1 to T3 groups, respectively. Patients in the T3 group showed the largest area at risk in comparison to patients in the lower platelet count tertiles on admission (►**Fig. 2B**). The infarct sizes in the 7- to 14-day scintigraphy (median) were 10.0% (IQR: 2.0–21.0%), 9.0% (IQR: 2.0–20.7%), and 12.0% of the left ventricle (IQR: 3.0–27.3%) in T1 to T3 groups, respectively. Again, the T3 group (T3) showed largest infarct sizes (►**Fig. 2C**). In line with these findings, peak CK-MB and troponin T values, both enzymatic estimates of infarct sizes, were highest in T3 (►**Supplementary Fig. S2A, B** [available in the online version only]). Peak CK-MB levels (median) were 107.5 U/L (IQR: 53.0–213.0 U/L) in the T1 group, 102.5 U/L (IQR: 41.0–193.0 U/L) in the T2 group, and 119.0 U/L (IQR: 61.0–272.0 U/L) in the T3 group. Peak troponin T levels (median) were 3.68 ng/mL (IQR: 1.32–7.04 ng/mL) in the T1 group, 3.0 ng/mL (IQR: 1.43–0.02 ng/mL) in the T2 group, and 4.61 ng/mL (IQR: 1.88–9.29 ng/mL) in the T3 group. The myocardial salvage index (median) was unchanged in between groups: 0.50 (IQR: 0.23–0.79), 0.53 (IQR: 0.27–0.81), and 0.48 (IQR: 0.26–0.80) in patients from groups T1, T2, and T3, respectively (►**Fig. 2D**).

Baseline Platelet Counts and Left Ventricular Function

An angiographic assessment of the LV-EF during the index procedure was available in 1,140 (95.2%) patients: 378 (94.0%) patients in the T1 group, 381 (96.2%) patients in the T2 group, and 381 (95.3%) patients in the T3 group. LV-EF (median) was 49.65% (IQR: 42.0–56.0%), 50.51% (IQR: 44.0–58.0%), and 49.0% (IQR: 41.0–56.0%) in the T1, T2, and T3 groups, respectively (►**Fig. 3A**). LV-EF was lowest in the T3 group. LV-EF measurements at 6-month follow-up were available in 468 (39.1%) of the patients: 144 (35.8%) patients in the T1 group, 152 (38.4%) patients in the T2 group, and 172 (43.0%) patients in the T3 group. At 6 months, LV-EF values (median) were 60.75% (IQR: 52.0–67.85%), 61.40% (IQR: 50.30–68.50%), and 56.0% (IQR: 47.0–67.0%) in the T1, T2, and T3 groups, respectively (►**Fig. 3B**). LV-EF was lowest in patients of the T3 group. Data on LV-EF both at baseline and 6-month follow-up were available for 409 patients (34.1%): 102 (25.4%) patients in the T1 group, 145 (36.6%) patients in the T2 group, and 162 (40.5%) patients in the T3 group. A significant recovery (improvement compared with baseline values) of the LV-EF at the 6-month follow-up angiography occurred in all groups regardless of the platelet count on admission (►**Fig. 3C**).

Baseline Platelet Counts and Clinical Outcomes

The median follow-up was 1,396 days. One- and 5-year follow-up for all-cause mortality was available for 1,069 (89.2%) and 449 (37.5%) patients, respectively. The primary endpoint (death of any cause at 1 year) occurred in 43 patients: 16 deaths in the T1 group, 5 deaths in the T2 group, and 22 deaths in the T3 group (Kaplan–Meier estimates of 1-year mortality: 4.2, 1.3, and 5.6%, respectively; log-rank test $p = 0.006$; ►**Fig. 4A**). At 5 years, deaths of any cause occurred in 103 patients: 39 deaths in the T1 group, 23 deaths in the T2 group, and 41 deaths in the T3 group (Kaplan–Meier estimates of 5-year mortality: 13.1, 8.0, and 12.4%, respectively; log-rank test $p = 0.057$; ►**Fig. 4B**). Mortality was lowest in the T2 group at both 1- and 5-year follow-up.

Table 1 Baseline and procedural characteristics

	T1 (102–206 [10^3/L])	T2 (207–259 [10^3/L])	T3 (260–921 [10^3/L])	*p*-Value
	***n* = 402 (33.6%)**	***n* = 396 (33.1%)**	***n* = 400 (33.4%)**	
Platelets on admission, mean [10^3/L] (SD)	176.70 (22.94)	231.78 (14.71)	309.96 (59.16)	<0.001
Age, years, mean (SD)	64.5 (12.3)	62.2 (13.3)	60.1 (13.0)	<0.001
Male sex, *n* (%)	344 (85.6)	306 (77.3)	264 (66.0)	<0.001
Diabetes, *n* (%)	83 (20.6)	73 (18.4)	72 (18.0)	0.592
BMI, mean in kg/m^2 (SD)	26.8 (3.6)	26.9 (3.8)	26.4 (4.3)	0.256
Hypercholesterolemia, *n* (%)	208 (51.7)	212 (53.5)	227 (56.8)	0.354
Hypertension, *n* (%)	286 (71.1)	270 (68.2)	285 (71.3)	0.562
Current smoking, *n* (%)	154 (38.3)	169 (42.7)	190 (47.5)	0.031
Family history, *n* (%)	139 (34.6)	171 (43.2)	166 (41.5)	0.031
CrCl, (mL/min) mean (SD)	83.9 (30.7)	89.2 (34.9)	89.6 (36.1)	0.031
No. of affected vessels				0.204
1, *n* (%)	128 (31.8)	149 (37.6)	149 (37.3)	
2, *n* (%)	124 (30.8)	119 (30.1)	130 (32.5)	
3, *n* (%)	150 (37.3)	128 (32.3)	121 (30.3)	
Previous MI, *n* (%)	61 (15.2)	47 (11.9)	41 (10.3)	0.098
Previous CABG, *n* (%)	17 (4.2)	15 (3.8)	5 (1.3)	0.032
Time to admission, hours, mean (SD)	6.9 (6.2)	6.3 (5.7)	6.7 (6.0)	0.303
Door to balloon, hours, mean (SD)	1.4 (0.8)	1.4 (0.9)	1.4 (0.8)	0.335
Killip class				0.464
I, *n* (%)	297 (73.9)	301 (76.0)	291 (72.8)	
II, *n* (%)	80 (19.0)	73 (18.4)	79 (19.8)	
III, *n* (%)	13 (3.2)	14 (3.5)	11 (2.8)	
IV, *n* (%)	12 (3.0)	8 (2.0)	19 (4.8)	
Baseline TIMI flow, *n* (%)				0.280
0, *n* (%)	188 (46.8)	182 (46.1)	194 (48.5)	
1, *n* (%)	36 (9.0)	57 (14.4)	43 (10.8)	
2, *n* (%)	104 (25.8)	87 (22.0)	86 (21.5)	
3, *n* (%)	74 (18.4)	69 (17.5)	77 (19.3)	
Type of PCI, *n* (%)				0.482
PTCA, *n* (%)	45 (11.2)	58 (14.6)	58 (14.5)	
Stenting, *n* (%)	357 (88.8)	338 (85.4)	342 (85.5)	
No reflow, *n* (%)	67 (16.7)	49 (12.4)	46 (11.5)	0.073
LV-EF, %, mean (SD)	48.8 (11.7)	50.0 (11.1)	48.4 (11.4)	0.121
Infarct vessel (culprit lesion)				0.011
Left main, *n* (%)	3 (0.7)	1 (0.3)	0 (0)	
LAD, *n* (%)	163 (40.5)	171 (43.2)	201 (50.3)	
LCX, *n* (%)	75 (18.7)	60 (15.2)	67 (16.8)	
RCA, *n* (%)	150 (37.3)	156 (39.4)	131 (32.8)	
CABG, *n* (%)	11 (2.7)	8 (2.0)	1 (0.3)	

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft surgery; CrCl, creatinine clearance; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LV-EF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; SD, standard deviation; T1, tertile 1; T2, tertile 2; T3, tertile 3; TIMI flow, thrombolysis in myocardial infarction flow.

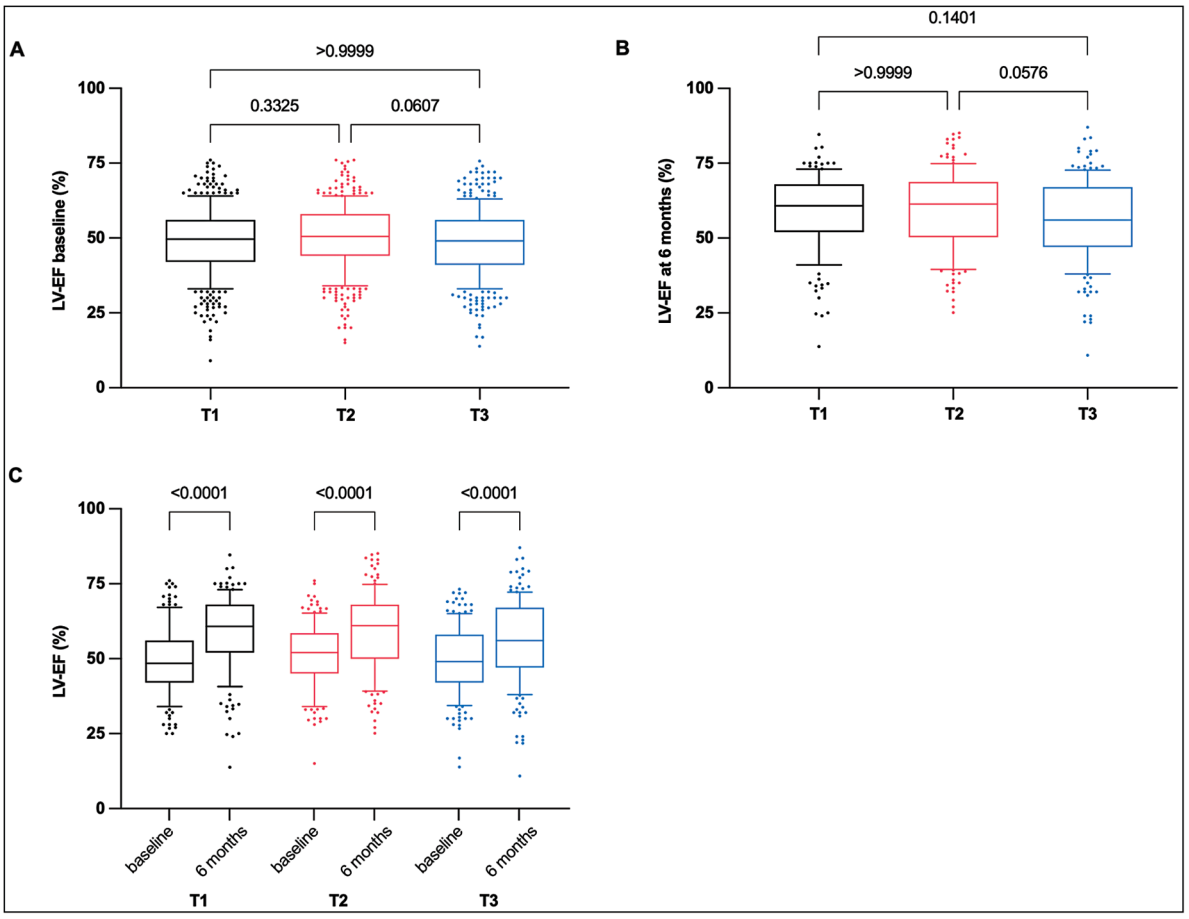

Fig. 3 Left ventricular ejection fraction (LV-EF) at (**A**) baseline, (**B**) 6 months, and (**C**) comparison between baseline and 6 months according to platelet count tertiles. Data are median with 25th–75th percentiles (boxes), 10th–90th percentiles (bars), and values outside the given percentiles (dots). T1, tertile 1; T2, tertile 2; T3, tertile 3.

At 1 year, MACE occurred in 300 patients: 98 events in the T1 group, 82 events in the T2 group, and 120 events in the T3 group (Kaplan–Meier estimates of 1-year MACE: 25.7, 21.3, and 30.8%, respectively; log-rank test, $p = 0.008$; ►**Supplementary Fig. S3A** [available in the online version only]). At 5 years, MACE occurred in 371 patients: 130 events in the T1 group, 102 events in the T2 group, and 139 events in the T3 group (Kaplan–Meier estimates of 5-year MACE: 37.9, 29.2, and 37.8%, respectively; log-rank test, $p = 0.017$; ►**Supplementary Fig. S3B** [available in the online version only]). The incidence of MACE was lowest in the T2 group.

At 1-year, non-fatal MIs occurred in 31 patients: 12 MIs in the T1 group, 6 MIs in the T2 group, and 13 MIs in the T3 group (Kaplan–Meier estimates of 1-year mortality: 3.2, 1.5, and 3,3%, respectively; log-rank test, $p = 0.166$; ►**Supplementary Fig. S4A** [available in the online version only]). At 5 years, MIs occurred in 40 patients: 16 MIs in the T1 group, 8 MIs in the T2 group, and 16 MIs in the T3 group (Kaplan–Meier estimates of 1-year mortality: 4.5, 2.4, and 4.7%, respectively; log-rank test, $p = 0.199$; ►**Supplementary Fig. S4B** [available in the online version only]). No difference was observed in between groups regarding the occurrence of MIs.

The association of baseline platelet counts with 1- and 5-year all-cause mortality and MACE was adjusted using Cox proportional hazard model (see methods for variables entered into the model).

Patients in the T1 and T3 groups of platelet count had a higher adjusted risk for all-cause death compared with patients of the T2 group (reference group): adjusted HR, 3.404 (1.226–9.542), $p = 0.019$ and 3.549 (1.228–9.782), $p = 0.014$, respectively, at 1 year. At 5-year follow-up, mortality was numerically higher in patients of the T1 and T3 groups compared with the T2 group (reference group): adjusted HR, 1.628 (0.960–2.759), $p = 0.071$ and 1.708 (0.996–2.926), $p = 0.052$, respectively; ►**Tables 2** and ►**Supplementary Table S2** [available in the online version only]).

Patients of the T3 group (but not those of the T1 group) had a higher risk of MACE at 1-year (adjusted HR, 1.530 (1.143–2.049), $p = 0.004$) and at 5 years of follow-up (adjusted HR: 1.447 (1.1.09–1.887), $p = 0.006$; ►**Tables 3** and ►**Supplementary Table S3** [available in the online version only]) compared with patients of the T2 group (reference group).

We also assessed whether high platelet counts are rather a marker of systemic inflammation induced by large infarcts or whether high platelet counts are causally related to the increased infarct size and ischemic risk. We tested the collinearity between platelet counts on admission and other inflammatory markers such as leukocyte counts (on

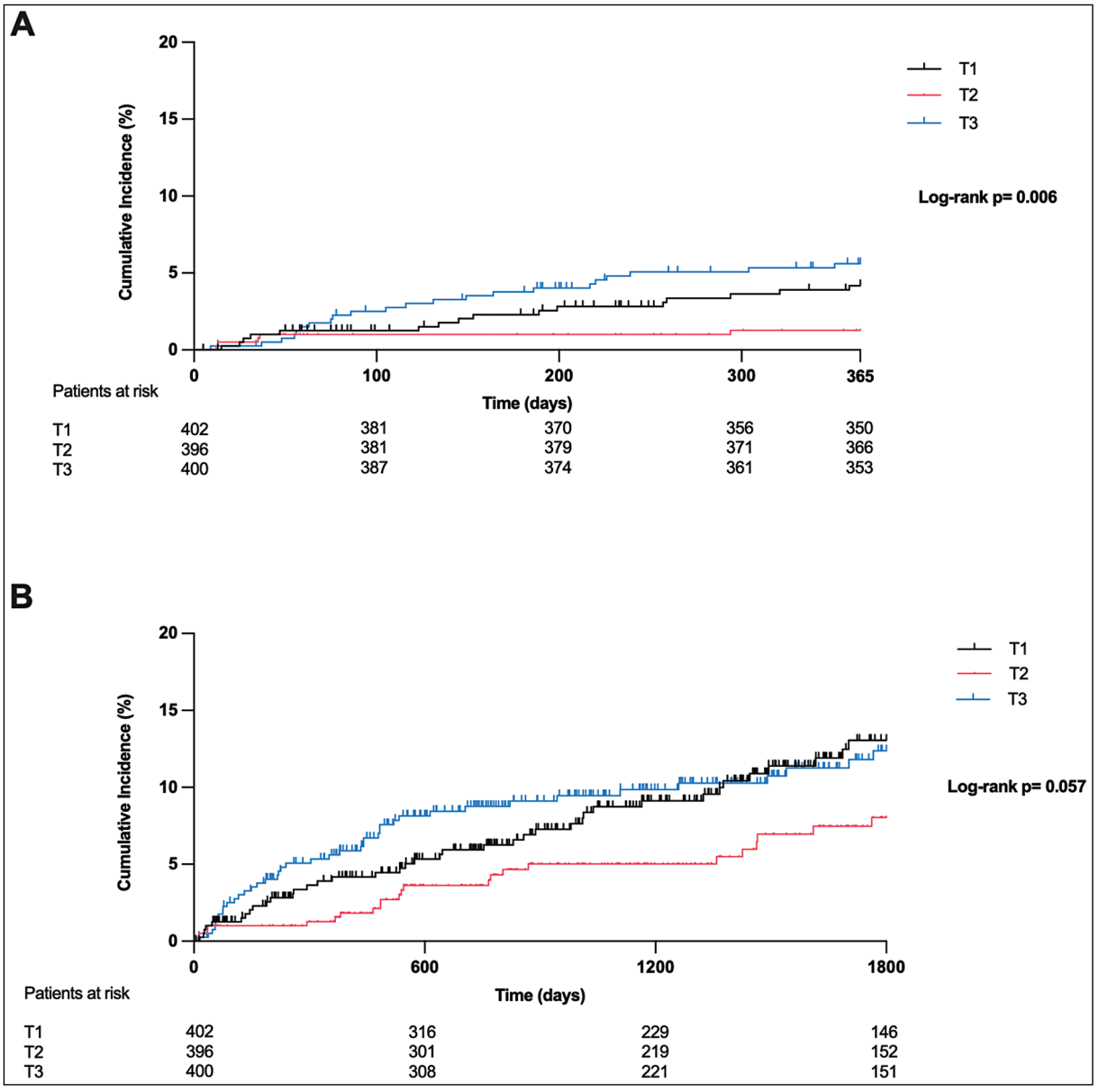

Fig. 4 Kaplan–Meier curves of 1-year (**A**) and 5-year (**B**) all-cause mortality according to platelet count tertiles. T1, tertile 1; T2, tertile 2; T3, tertile 3.

Table 2 The association of platelet count on admission with 1-year and 5-year all-cause mortality after adjustment in the multivariable Cox proportional hazard model

	1-year mortality HR (95% CI)	*p*-Value	5-year mortality HR (95% CI)	*p*-Value
Tertile 1	3.404 (1.226–9.542)	0.019	1.628 (0.960–2.759)	0.071
Tertile 2	Reference		Reference	
Tertile 3	3.549 (1.228–9.782)	0.014	1.708 (0.996–2.926)	0.052

Abbreviations: CI, confidence interval; HR, hazard ratio.
Note: Age, heart rate (on admission), systolic blood pressure (on admission), creatinine clearance, sex, diabetes, Killip class (on admission), previous myocardial infarction, number of diseased vessels, platelet levels on admission were entered into the analysis.

admission and day 1 after MI) or C-reactive protein (CRP) levels (on admission and day 1 after MI). Although significant correlations were detected between these variables, Pearson's correlation coefficients remained <0.3 and variance inflation factors were <6 for all comparisons (►**Supplementary Tables S4–S5** [available in the online version only]) suggesting an insignificant collinearity. Therefore, leukocyte counts and CRP values were entered into the

Table 3 The association of platelet count on admission with 1-year and 5-year MACE after adjustment in the multivariable Cox proportional hazard model

	1-year MACE HR (95% CI)	*p*-Value	5-year MACE HR (95% CI)	*p*-Value
Tertile 1	1.199 (0.889–1.618)	0.235	1.268 (0.973–1.652)	0.079
Tertile 2	Reference		Reference	
Tertile 3	1.530 (1.143–2.049)	0.004	1.447 (1.109–1.887)	0.006

Abbreviations: CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events.
Note: Age, heart rate (on admission), systolic blood pressure (on admission), creatinine clearance, sex, diabetes, Killip class (on admission), previous myocardial infarction, number of diseased vessels, platelet levels on admission were entered into the analysis.

multivariable Cox proportional hazard models alongside other baseline variables. The associations between platelet count on admission and clinical outcomes persisted after including these markers of systemic inflammation at baseline or on day 1 after MI (►**Supplementary Tables S6–S17** [available in the online version only]). These findings suggest that platelet levels may not only be elevated as part of the inflammatory response induced by large infarcts.

Discussion

Platelets are physiological inhibitors of bleeding from healthy blood vessels (hemostasis) but can also function as pathological instigators of occlusive events in diseased blood vessels (thrombosis).[2] MI occurs as a consequence of atherosclerotic plaque rupture/erosion resulting in atherothrombosis which blocks the supply of oxygenated blood to the heart.[3,4] Studies investigating the association of baseline platelet counts with myocardial infarct size, left ventricular function, and clinical outcome in STEMI patients are scarce. We here report results from a large STEMI cohort that combines (1) scintigraphic and enzymatic estimates of infarct size and salvage, (2) left ventricular function at the time of PPCI and 6 months thereafter, and (3) long-term (5 years) clinical outcomes (death of any cause and MACE). We found that STEMI patients with highest baseline platelet count showed greatest infarct size, while STEMI patients with both highest and lowest baseline platelet count showed increased mortality.

Our study showed that patients with higher platelet counts showed the greatest myocardial area at risk (the ischemic proportion of the myocardium after coronary occlusion) as assessed by the first round of SPECT imaging. These data suggest that higher platelet counts may be related to larger ischemic areas and an increased thrombotic burden. Apart from larger initial ischemic areas of the myocardium, we also found an association between higher baseline platelet counts and larger final infarct sizes in the repeat SPECT imaging. These findings were further corroborated by finding associations between platelet counts and other markers of infarct size (peak CK-MB and cardiac troponin T). Although platelet count correlated with the extent of myocardial ischemia and injury, it was not associated with myocardial salvage after PPCI. These findings may indicate that platelets impact ischemia (which is caused by atherothrombosis) but not myocardial rescue or recovery (which may be modified by thromboinflammation). To our knowledge, this study is the first to address the association between platelet count and myocardial ischemia in patients with STEMI.

Since patients with higher platelet counts had larger infarct sizes, the strongest reduction in the left ventricular function was observed in this group. Although the correlations were close to being significant, the threshold of statistical significance was not achieved. These findings are in line with a previous publication reporting that patients with STEMI and higher platelet counts had reduced left ventricular systolic function both on admission and before discharge.[15] Our study found an association between platelet count on admission and mortality, which may be explained by larger initial areas at risk and infarct sizes, and more depressed left ventricular function associated with higher platelet counts. Our finding that higher platelet counts correlate with higher mortality is in line with observations of Nikolsky et al who found an independent association between a higher baseline platelet count and risk of death within the first year after PCI in patients with AMI (mainly STEMI).[9] Accordingly, Iijima et al showed that a higher platelet count was an independent correlate of 30-day mortality after PCI in patients with coronary artery disease.[10] Furthermore, Ly et al observed that higher platelet counts were associated with higher rates of adverse clinical outcomes in patients with STEMI at 30 days.[16] Several studies have reported a **U**-shaped association between platelet counts (thrombocytosis and thrombocytopenia) and mortality in patients with ACS. Song et al showed that both low and high platelet counts were associated with an increased risk of all-cause mortality at 2 years in patients with acute STEMI or NSTEMI.[7] Małyszczak et al reported that both thrombocytopenia and thrombocytosis on admission in post-ACS patients were associated with a higher 5-year mortality rate.[8] Mueller et al found that patients with unstable angina/NSTEMI and a platelet count between 181 and 210×10^9/L had reduced mortality compared with patients with lower or higher platelet counts.[11] These findings agree with our results showing increased mortality in patients with both highest and lowest baseline platelet counts. Unlike in the T3 group, we did not find any signal for an impact on the ischemic area, infarct size, and LV function in the T1 group. This, together with the fact that MACE was also not changed in the T1 group, may lead to the assumption that the increased mortality observed in the T1 group may be unrelated to the qualifying event (STEMI) and a consequence of another underlying disorder. While an increased atherothrombotic risk in patients with high platelet counts may be suggested, a

divergent pathomechanism likely contributes to increased mortality in patients with low platelet counts.

Our study raises the question whether platelet counts directly impact the pathophysiology of myocardial ischemia/necrosis or whether platelet counts are rather a marker of systemic inflammation and the inflammatory response in the acute phase of MI. The fact that the association between the platelet counts on admission and clinical outcome persisted after the adjustment for traditional markers of systemic inflammation, such as leukocyte count and CRP, may suggest that platelets indeed play a direct role in the pathophysiology of ischemia/necrosis. A study by Tucker et al, in which a mild reduction of platelet counts without modulating platelet function reduced occlusive thrombogenesis in a non-human primate model, appears to support this hypothesis.[17] Furthermore, our data showed that a higher platelet count was associated with a higher risk of mortality at 1 year but not at 5 years after PPCI. We speculate that this may be explained by the fact that platelets seem to more affect acute ischemia than recovery after MI (i.e., rather immediate than long-term events). However, this hypothesis requires further exploration.

Limitations

Our study has several limitations. First, this study represents a retrospective analysis from an observational study and not from a prospective clinical trial dedicated to investigating the association of platelet numbers and outcome in patients with STEMI. In this regard, the study findings should be considered as hypothesis-generating. Second, since our study enrolled patients between 2002 and 2007, antiplatelet therapy, although similarly used in between the three groups, was somewhat outdated (was restricted mostly to clopidogrel) and potent P2Y12 inhibitors were not administered. Consequently, our results may not be transferable to patients who receive contemporary state-of-the-art treatment including more potent antiplatelet therapy.

Third, only platelet counts were assessed and data on platelet phenotypes or reticulated platelets were not available. Hence, we cannot exclude the possibility that the activation state of platelets might have contributed to our findings. Fourth, although recommendations on the duration of antiplatelet therapy were based on the guidelines, we cannot exclude that patients with lower platelet counts received shorter antiplatelet therapy in the ambulatory setting. Fifths, data on bleeding events were not available. This may have been of particular interest in the low platelet count group. Here, bleeding may have been promoted by low platelet numbers or may have caused low platelet numbers due to platelet consumption. Moreover, data on the management of bleeding including blood cell transfusions (e.g., administration of red blood cell and/or platelet concentrates) or platelet function in this group are missing.

Conclusion

In patients with STEMI undergoing PPCI, platelet count at baseline was associated with initial area at risk, final infarct size, and mortality. Thus, baseline platelet count may represent a prognostic marker after acute MI. As myocardial salvage by PPCI was not influenced by platelet count, baseline platelet count appears to be involved in the initiation of myocardial ischemia (serving as a correlate of ischemia and necrosis extent) rather than in the myocardial recovery after MI.

What is known on this topic?

- Platelets are important players in hemostasis and thrombosis and contribute to the development and exacerbation of cardiovascular disease.
- Elevated platelet counts on admission were found to be associated with adverse clinical outcomes in patients with acute myocardial infarction.
- Data on the impact of platelet counts on myocardial ischemia and recovery together with outcome in patients with acute ST-segment elevation myocardial infarction are scarce.

What does this paper add?

- In a large cohort of STEMI patients, those with highest baseline platelet count showed greatest infarct size.
- STEMI patients with both highest and lowest baseline platelet count showed increased mortality.
- Our data suggest that higher platelet counts may be related to larger ischemic areas and an increased thrombotic burden.

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Conflict of Interest

None declared.

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