



Baseline Platelet Count and Clinical Outcome in Acute Coronary Syndrome

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Background: It is unclear whether platelet count (PLT) is independently associated with clinical outcome in patients with acute coronary syndrome (ACS).

Methods and Results: MEDLINE, EMBASE, the Cochrane library clinical trials registry, ISI Science Citation Index, and ISI Web of Knowledge were searched, supplemented by hand-scanning of references of relevant publications and contacting content experts. Eight studies including 39,324 patients were identified that addressed the following issues: major adverse cardiac events (MACE) and mortality were defined as endpoints; the relative risk (RR) or relative odds and their variance with MACE associated with PLT; studies in which only PLT was quantified. Two investigators independently abstracted information on study design, study and participant characteristics, PLT, clinical outcomes, control for potential confounding factors and risk estimates using a standardized protocol. At 1-month follow-up, compared with the bottom PLT group ($<150 \times 10^9/L$), the pooled RRs of mortality and MACE were 1.78 ($P=0.14$) and 1.63 ($P<0.001$) for the upper PLT ($>350 \times 10^9/L$), respectively. At long-term follow-up (≥ 1 year), the pooled RRs of mortality and MACE were 1.48 ($P=0.02$) and 1.28 ($P=0.02$) for the upper PLT, respectively. Moreover, the pooled RR of longitudinal mortality was 1.024 ($P=0.03$) when PLT was used as a continuous variable.

Conclusions: Higher PLT at baseline increases the RR of mortality and MACE in ACS patients. (*Circ J* 2012; **76**: 704–711)

Key Words: Acute coronary syndrome; Major adverse cardiac events; Meta-analysis; Mortality; Platelet count

Platelet-induced inflammatory processes might play a critical role in atherothrombosis.^{1–4} Indeed, anti-platelet drugs have been associated with a decrease in adverse cardiovascular events, which also highlights the role of the platelet in atherosclerosis.^{5–8} Although there are a variety of methods to test platelet function, most of them are expensive, time-consuming, and require specialized equipment in the laboratory. In a previous meta-analysis, mean platelet volume (MPV), a common index of platelet size, had been independently associated with cardiovascular events.⁹ Platelet count (PLT) itself is a simple test that is more widespread than MPV. Higher PLTs have been considered to be associated with adverse outcomes in acute coronary syndrome (ACS) patients;^{10–12} furthermore, the relationship may be curvilinear or U shaped, and to this end Overgaard et al reported that thrombocytopenia at baseline is also a predictor of in-hospital mor-

tality.¹³ Given the complexity of this relationship, the aim of the present study was to more fully evaluate the relationship between PLT and the risk estimates of clinical outcome in ACS patients both at short-term and long-term follow-up.

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Methods

Data Sources, Search Strategy, and Selection Criteria

Systematic literature searches were conducted of 5 databases: Medline, the Cochrane Library, EMBASE, ISI Science Citation Index, and ISI Web of Knowledge up to October 2010. The search term “PLT” was used in combination with “ACS”, “coronary artery disease (CAD)”, “percutaneous coronary intervention (PCI)”, “predictive”, “prognostic”. The references

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Table 1. Characteristics of Included Studies

Study	Country	Original design	Included trials (registered)	No. patients	Mean age (years)	Male%	Follow-up	Disease at baseline
Sjaauw et al, 2006 ²²	Netherlands	Retrospective cohort	–	264	67	62	30 days	AMI
Ly et al, 2006 ¹¹	USA	Pooled RCTs	TIMI4, 9A, 9B, 10A, 10B, 12, 14, 16, 20, 23, 24 trials	10,793	59	77	30 days	STEMI
Gibson et al, 2006 ¹⁰	USA	RCT	TIMI28 trial	3,491	58	81	30 days	STEMI
Mueller et al, 2006 ²³	Germany	Prospective cohort	–	1,616	64	71	17 months	UA/NSTEMI
Nikolsky et al, 2007 ²⁰	USA	RCT	CADILLAC	2,082	59	75	30 days, 1 year	AMI
Overgaard et al, 2008 ¹³	Canada	Cohort	–	10,821	63	73	In hospital	CAD STEMI, Non-AMI
Mahaffey et al, 2008 ²¹	Europe, USA	RCT	SYNERGY	9,978	67	66	30 days, 1 year	ACS
Wu, 2010	China	Cohort	–	279	62	68	30 days, 1 year, 3 years	STEMI

Study	Treatment	Anti-platelet usage	Clinical outcomes	Adjusted by coronary risk factors	No. quality markers included
Sjaauw et al, 2006 ²²	Thrombolysis, PCI, CABG	Aspirin, Thienopyridine partly	All-cause mortality, Re-infarction	Gender, hypertension, PMI and other baseline clinical variables	10
Ly et al, 2006 ¹¹	Thrombolysis, PCI, CABG	Aspirin, Thienopyridine partly	All-cause mortality	Age, gender, weight, history of diabetes and smoking and other baseline clinical variables	11
Gibson et al, 2006 ¹⁰	Thrombolysis, PCI, CABG	Aspirin, Clopidogrel	Re-infarction	Gender, history of hypertension, diabetes, smoking, time from symptom onset to fibrinolytic treatment, and initial type of heparin used, and clinical correlates of poorer outcomes in STEMI	11
Mueller et al, 2006 ²³	PCI, CABG	Aspirin, Thienopyridine partly (50%)	All-cause mortality, MACEs	All baseline demographic, clinical, and angiographic variables	11
Nikolsky et al, 2007 ²⁰	Primary PCI	Aspirin, Thienopyridine partly (2.7%)	All-cause mortality	All baseline variables included (such as age, gender, diabetes, hypertension, hypercholesterolemia, smoking, PMI, Killip class, creatinine clearance, LVEF)	12
Overgaard et al, 2008 ¹³	PCI	Aspirin, GP IIb/IIIa use (88%)	All-cause mortality, MACEs, Bleeding	Age, renal insufficiency, PMI, LVEF, multi-vessel disease	10
Mahaffey et al, 2008 ²¹	PCI, CABG	Aspirin, Clopidogrel	All-cause mortality	All potential baseline covariates included (such as age, sex, weight, height, race, smoking, Cr clearance, Killip class, blood pressure)	10
Wu, 2010	PCI	Aspirin, Clopidogrel	All-cause mortality, MACEs	Age, gender, PMI, diabetes, hypertension, smoking and other baseline variables	10

AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; RCT, randomized controlled trial; TIMI, Thrombolysis In Myocardial Infarction; UA, unstable angina; CAD, coronary artery disease; GP, glycoprotein; MACE, major adverse cardiac event; LVEF, left ventricular ejection fraction.

sections of reviews and original articles were also scanned for trials missed in the primary searches.

We included articles if they met all the following criteria: (1) all patients had CAD and the data on ACS patients could be extracted; (2) PLT on admission was available; (3) the clinical outcomes of interest were all-cause mortality and major adverse cardiac events (MACE); (4) relative risk (RR) estimates and their 95% confidence intervals (95%CI) were given or sufficient data were available to calculate these numbers; (5) follow-up duration was ≥ 1 month; and (6) the study was designed as a random clinical trial or cohort study.

Data Extraction and Study Quality

Two reviewers (Y.H.W. and H.W.) independently extracted

study characteristics using standardized forms: we identified 9 articles including 22 trials, and 1 study in our own center was extracted (Wu 2010), but the data of ACS patients in 2 articles (Vidwan et al¹⁴ and Lijima et al¹²) could not be extracted after contacting authors, finally, there was a total of 18 trials included in the meta-analysis. We extracted the reported RR, odds ratio or hazard ratio, and 95% CIs from each study: if the information was insufficient, we contacted the content experts for further analysis.

We assessed the quality of each study according to modified criteria based on the criteria constructed by Hemingway et al^{15,16} (a total of 15 items relating to the pre-specified research question, population at start and end of follow up, biomarker measurement, outcome assessment, confounder measurement,

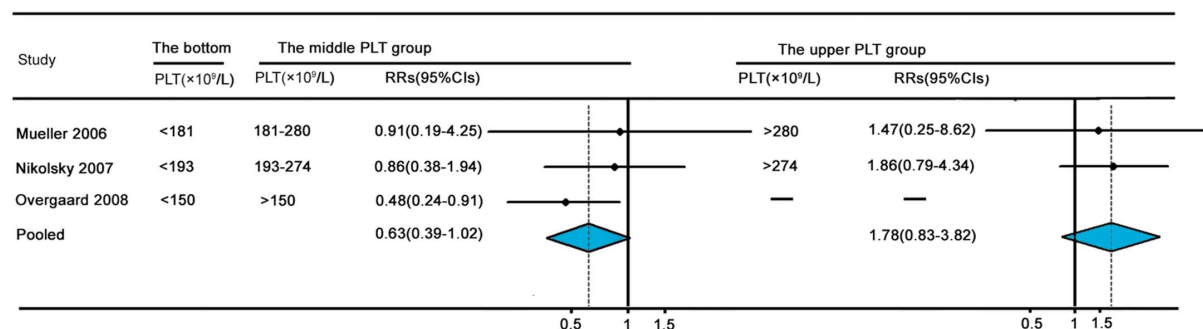
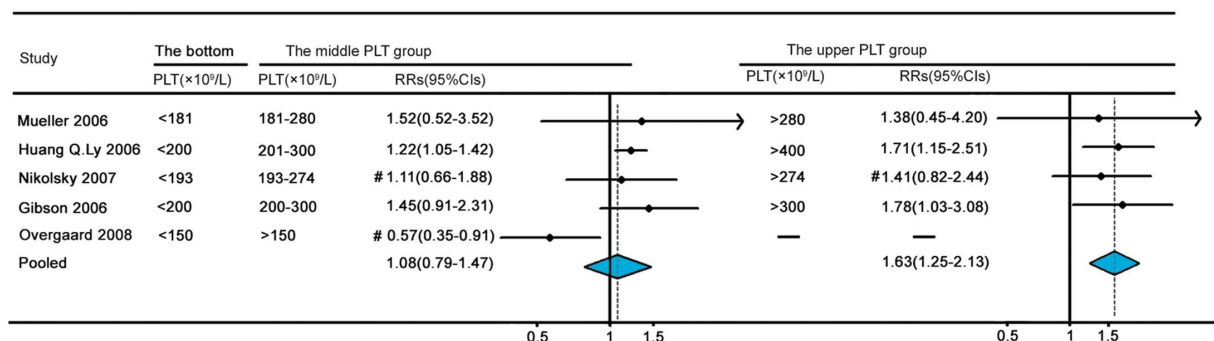
A**B**

Figure 1. Prognostic value of platelet count (PLT) at 1-month follow-up. **(A)** Predictive value of PLT for 1-month mortality. **(B)** Predictive value of PLT for 1-month major adverse cardiac events. #Crude relative risk (RR) not adjusted by confounders. CI, confidence interval.

and analytic choices; [Table S1](#)).

Data Synthesis and Statistical Analysis

Separate meta-analyses were conducted for the included studies reporting the risk estimates of categorical and continuous PLT. The first type of studies (referring to categorical PLT) were classified into 3 groups according to the Laboratory Reference Value suggested:¹⁷ the bottom group ($<150 \times 10^9/L$), the middle group ($150\text{--}350 \times 10^9/L$), and the upper group ($>350 \times 10^9/L$). The category-specific risk estimates of each study were assigned to the standardized categories according to the mid-point for closed categories or the median (or the corresponding median previously defined as 20% lower than the lowest cut-off point and 20% higher than the highest cut-off point) for the open categories, as 1 previous meta-analysis adopted.¹⁸ The pooled estimates were extracted for the overall effect analysis.

A fixed-effect model with the Mantel-Haenszel method was used to pool these RRs. The extent of heterogeneity across studies was checked using the chi-square test and I^2 test (I^2 test quantifies the proportion of total variation across studies due to heterogeneity rather than chance); $P \leq 0.10$ in combination with $I^2 > 50\%$ indicates significant heterogeneity, and the random-effect model was used if heterogeneity was present.

We analyzed the dose-response relationship using linear, first-order, and second-order fractional polynomial regression of the inverse variance-weighted data to estimate a curve of best fit.¹⁹ Best-fit curves were selected using decreased deviance compared with the reference model. Comparisons of curves to determine best fit were done using a chi-square dis-

tribution.¹⁹

Sensitivity analyses were performed to ascertain the effects attributable to the single study in which PLT were divided into 2 segments according to the lower limit. As for the clinical outcome of patients at 1-month follow-up, subgroup analyses could be used to assess the source of heterogeneity by different end events (all-cause death, major cardiac events), confounder adjustment (adjusted or not), mean age (<60 years, ≥ 60 years). To assess for publication bias, funnel plots (ie, plots of study results against precision) were constructed. Egger's regression test was adopted to test the asymmetry of funnel plots. All analyses were conducted using Stata software (version 11.0; StatCorp, College Station, TX, USA).

Results

Study Characteristics and Data Quality

Eight studies (encompassing 18 trials) with 39,324 patients were included in our meta-analysis, as detailed in [Figure S1](#). Among the 8 studies, 4 were the secondary analyses of registered randomized controlled trials,^{10,11,20,21} while the others were cohort studies. All studies were conducted in Europe or USA, with the exception of our previous study. Mean patient age ranged from 58 to 67 years; mean follow-up ranged from 30 days to 3 years. Disease at baseline was ACS in 8 studies;^{10,11,20–23} Overgaard et al reported the outcomes of ACS and non-ACS patients, respectively.¹³ The quality of the included studies was assessed using a modified method ([Table S1](#)). All studies were high quality, as indicated in [Table 1](#).

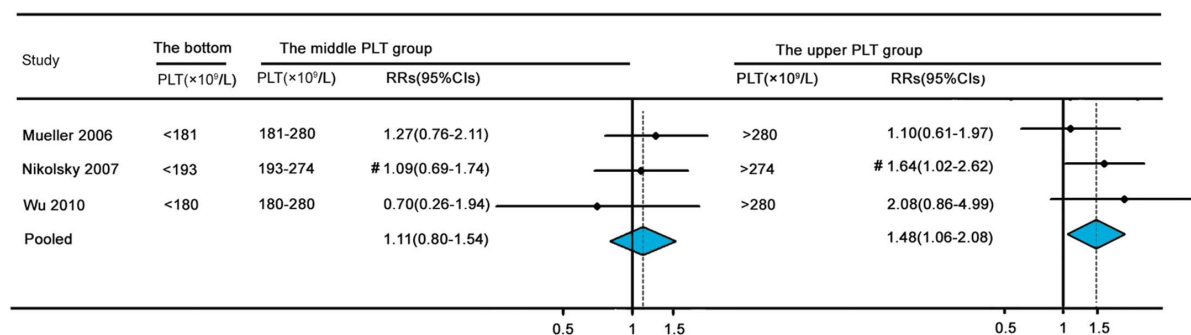
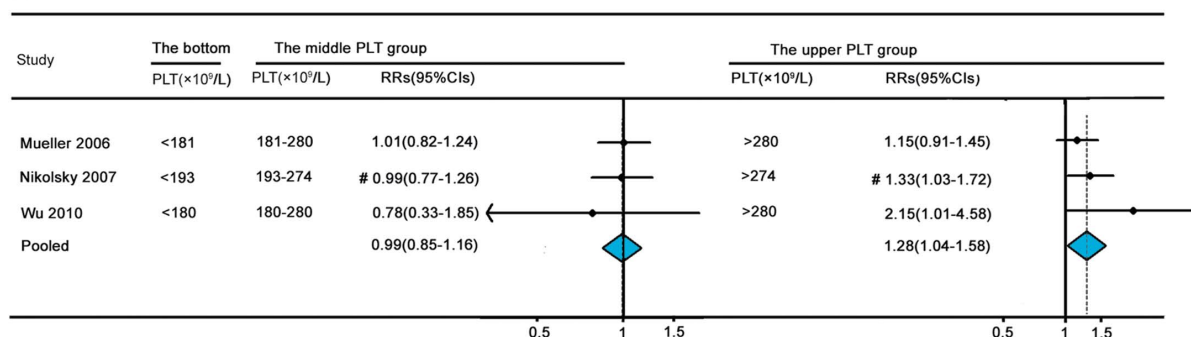
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Figure 2. Prognostic value of platelet count (PLT) at long-term follow-up. **(A)** Predictive value of PLT for longitudinal mortality. **(B)** Predictive value of PLT for longitudinal major adverse cardiac events. #Crude relative risk (RR) not adjusted by confounders. CI, confidence interval.

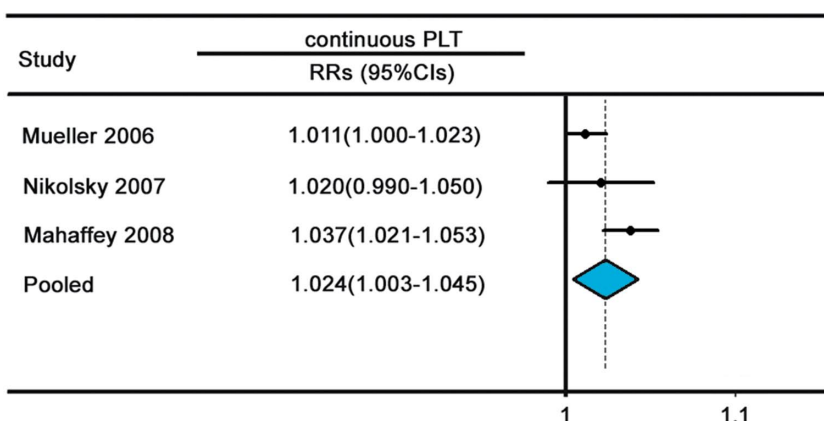


Figure 3. Prognostic value of continuous platelet count (PLT) for mortality at longitudinal follow-up. CI, confidence interval; RR, relative risk.

Predictive Value of Categorical PLT

Separate meta-analyses were conducted for 1-month and long-term outcomes (≥ 1 year).

At 1-month follow-up, a total of 25,365 patients were included. When mortality was used as the outcome, P-value for heterogeneity was 0.50 and 0.82, and I^2 was 0% and 0% for the middle and upper PLT category, respectively. Compared to the bottom group, combined RR (95%CI) was 0.63 (0.39–1.02) for the middle group and 1.78 (0.83–3.82) for the upper group. When MACE was used as the outcomes, the P-value for heterogeneity was 0.04 and 0.92, and I^2 was 61.2% and 0% for the

middle and upper PLT category, respectively. Compared to the bottom group, the combined RR (95%CI) was 1.08 (0.79–1.47) for the middle group and 1.63 (1.25–2.13; $P < 0.001$) for the upper group. Overall results are shown in [Figure 1](#).

At long-term follow-up (≥ 1 year), 13,955 patients were included. When mortality was used as the outcome, the P-value for heterogeneity was 0.59 and 0.42, and I^2 was 0% and 0% for the middle and upper PLT category, respectively. Compared to the bottom group, the combined RR (95%CI) was 1.11 (0.80–1.54) for the middle group and 1.48 (1.06–2.08) ($P = 0.02$) for the upper group. When MACE were used as the

Table 2. Predictive Value for 1-Month Major Adverse Events vs. PLT Level

	Bottom PLT [<150×10 ⁹ /L]	Middle PLT [150–350×10 ⁹ /L]		Upper PLT [>350×10 ⁹ /L]	
	RR	No. patients	RR (95%CI)	No. patients	RR (95%CI)
Clinical outcomes					
All-cause death	1.00	14,519	0.63 (0.39–1.02)	3,698	1.78 (0.83–3.82)
Major adverse cardiac events	1.00	28,831	1.08 (0.79–1.47)	18,010	1.63 (1.25–2.13)*
Confounder adjustment					
Unadjusted	1.00	12,903	0.79 (0.41–1.52) [†]	2,082	1.41 (0.82–2.44)
Adjusted	1.00	15,928	1.24 (1.08–1.43)**	15,928	1.70 (1.25–2.31)***
Mean age (years)					
<60	1.00	16,394	1.23 (1.07–1.41)**	15,928	1.65 (1.25–2.17)***
≥60	1.00	12,437	0.79 (0.35–1.80) [†]	2,082	1.38 (0.45–4.20)
Ethnicity					
Caucasian	1.00	28,831	1.08 (0.79–1.47)	18,010	1.63 (1.25–2.13)*
Asian	1.00	279	0.87 (0.18–2.76)	279	3.51 (1.21–6.77)**

[†]Random-effects model was used. *0.01≤P<0.05; **0.001≤P<0.01; ***0.01≤P<0.001.

PLT, platelet count; RR, relative risk; CI, confidence interval.

outcome, the P-value for heterogeneity was 0.91 and 0.26, and I² was 0% and 26.0% for the middle and upper PLT category, respectively. Compared to the bottom group, the combined RR (95%CI) was 0.99 (0.85–1.16) for the middle group and 1.28 (1.04–1.58; P=0.02) for the upper group. Overall results are shown in **Figure 2**.

Predictive Value of Continuous PLT

The predictive value of continuous PLT was available in 4 studies (The results of 2 studies were published, and the remaining results were calculated with original data). At 1-month follow-up, the result of Thrombolysis In Myocardial Infarction (TIMI) trials¹¹ (n=10,793, provided by Gibson and Murphy) indicated that PLT is an independent predictor for 1-month mortality (RR, 1.002; 95%CI: 1.0007–1.003; P=0.001) and 1-month MACE (RR, 1.002; 95%CI: 1.001–1.003; P<0.001) but has no independent predictive value for 1-month myocardial infarction (RR, 1.001; 95%CI: 1.0–1.003; P=0.056), or 1-month congestive heart failure (RR, 1.0014; 95%CI: 1.0–1.003; P=0.054). Nikolsky et al (n=2,082) also reported that PLT at baseline has independent predictive value of re-infarction at 1-month follow-up (RR, 1.08; 95%CI: 1.02–1.12; P=0.008).²⁰ Another study including 264 patients conducted by Sjaauw et al (n=264), however, reported that PLT had no independent predictive value of mortality as a continuous variable (RR, 0.996; 95%CI: 0.991–1.001).²²

At long-term follow-up (≥1 year), we conducted a meta-analysis in which PLT was used as a continuous variable adjusted by confounders.^{20,21,23} The results indicated that continuous PLT is an independent predictor for longitudinal mortality (RR, 1.024; 95%CI: 1.003–1.045; P=0.03; **Figure 3**). As for longitudinal cardiovascular events, Nikolsky et al (n=2,082) also reported that continuous PLT is an independent predictor for death/reinfarction.²⁴

Sensitivity and Subgroup Analysis

To explore the potential impact of within-study heterogeneity, we conducted subgroup and sensitivity analyses. After removing the single study in which PLTs were divided into 2 segments,¹³ the pooled RR of mortality changed from 0.63 (95%CI: 0.39–1.02) to 0.87 (95%CI: 0.42–1.79), and the pooled RR of MACE changed from 1.08 (95%CI: 0.79–1.47) to 1.23 (95%CI: 1.08–1.41; P=0.003) for the middle PLT cat-

egory at 1-month follow-up, with a significant decrease in heterogeneity from I²=61% to I²=0%.

Subgroup analyses were available in the patients at 1-month follow-up. We found that the pooled risk estimate adjusted for confounders was significantly higher than that without adjusting in the top PLT group (RR=1.70 vs. RR=1.41; P<0.01), and in the middle PLT group (RR=1.24 vs. RR=0.79; P<0.01). Moreover, the pooled RRs in patients aged <60 years seemed to be higher than in those aged >60 years in the top PLT group (RR=1.65 vs. RR=1.38; P<0.01). Overall results are given in **Table 2**.

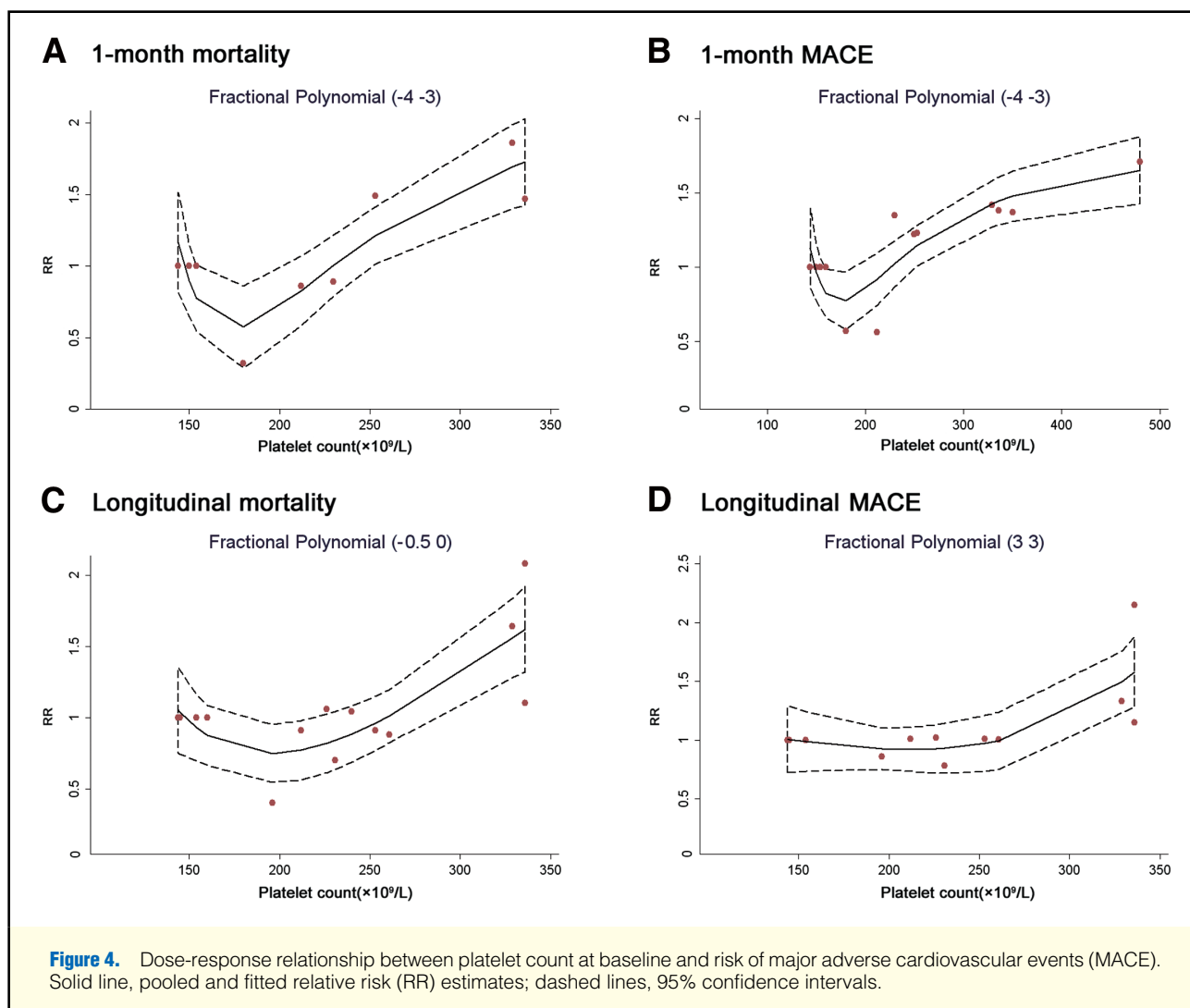
Publication Bias

Begg's funnel plot and Egger-weighted regression indicated that there is no significant publication bias in clinical outcome at 1-month follow-up for either the middle PLT group or the upper PLT group (P_{Egger}=0.33 and P_{Egger}=0.07, respectively). Significant publication bias was not observed in clinical outcome at long-term follow-up for the upper PLT group (P_{Egger}=0.68), but may affect the middle PLT group (P_{Egger}=0.02; **Figure S2**).

Discussion

This is the first meta-analysis to assess the relationship between PLT and cardiovascular risk; it included 8 studies consisting of 39,324 patients. There were 2 major findings in the present study. First, higher PLT was associated with significantly higher risk of MACE/mortality as compared with the bottom PLT either at 1-month or longitudinal follow-up in ACS patients. Second, a U-shaped relationship was observed between PLT per unit and risk of MACE/mortality (**Figure 4**).

Subgroup analyses were performed to investigate the potential sources of heterogeneity in clinical outcome at 1-month follow-up. We confirmed the predictive value of higher PLT in ACS, but we could not obtain an analogous finding in stable CAD because of insufficient data. Furthermore, the top PLT count was an independent predictor in those younger patients (mean age <60 years), more so than the older patients (mean age >60 years), thus age might be one of the factors affecting the predictive value of higher PLT. At long-term follow-up, our meta-analyses confirmed the prognostic value of the top PLT in ACS patients also, which was consistent with the



results of meta-analysis when PLT was used as a continuous variable (Figures 3,4).

Acquired thrombocytopenia was considered to be associated with worse outcome in patients who underwent some cardiac procedures and received some medications (especially in those PCI patients with glycoprotein IIb/IIIa inhibitor and heparin),^{24–26} thus it is important to be aware of the potential adverse outcome induced by thrombocytopenia at baseline ($<150 \times 10^9/L$). Although the trend of protective effect of middle PLT as compared with the bottom PLT was seen in several studies,^{11,12,20,23} a single study demonstrating that thrombocytopenia at baseline is an independent predictor was conducted by Overgaard et al in 2008.¹³

Explanations of the prognostic value of PLT might require multiple mechanisms. First, the role of platelets in the inflammation at a local vascular level might partially account for the results.^{1,2} Previous studies have indicated that platelets are activated and aggregate more easily in culprit vessels of CAD patients,²⁷ especially in those patients with ACS.^{28,29} Activated platelets release inflammatory and mitogenic mediators into the local microenvironment, such as adhesion protein (eg, fibrinogen), growth factors (eg, platelet-derived growth factor, endothelial growth factor), chemokines (eg, platelet factor-4), cytokine-like factors (eg, interleukin-1 β , CD 40 ligand) and

coagulation factors (eg, factor V), which would promote the recruitment of more platelets and leukocytes.^{2,30} Therefore, elevated PLT at baseline might aggravate the inflammatory state, which is considered to result in more adverse outcome.^{20,31} Moreover, recent studies have demonstrated that platelet-leukocyte conjugates play a prominent role in the etiology of CAD,^{32–35} and leukocyte count has been accepted as an independent predictor for ACS either at short-term or long-term follow-up.^{36–40} Because PLT was considered to be significantly correlated with formation of platelet-leukocyte conjugates and with P-selection expression both at baseline and upon stimulation,⁴¹ it could be suggested that PLT might simply be a predictor of outcome in ACS by representing the formation of platelet-leukocyte conjugates as leukocyte count did. The relationship between thrombocytopenia at baseline and ACS outcome is complex and inconclusive, recent studies have shown that not only hereditary thrombocytopenia^{42–45} but also several medications might account for it, such as the use of platelet glycoprotein IIb/IIIa receptor inhibitors, heparin, and intra-aortic balloon pump.²⁵ Some studies found that the thrombocytopenia patients were more likely to be diabetic, have a worse baseline left ventricular ejection fraction and a greater likelihood of 3-vessel disease,^{13,46} which might lead to adverse events. Furthermore, the thrombocytopenia patients

had a significantly higher prevalence of bleeding complications, which in turn were associated with increased risk of all-cause mortality and MACEs in ACS patients.⁴⁷ The mechanism associated with upper PLT might explain why the interaction curve is U-shaped between PLT and cardiovascular events, nevertheless, further studies are required.

The present study and meta-analysis have several strengths. First, we used different search methods and included a large number of patients, sufficient to allow adequate statistical power to calculate the results obtained. Second, all the included studies were of high methodological quality for analysis. Third, most of the risk estimates were confounder adjusted in the dose dependence curves to eliminate potential bias. Finally, we performed a subgroup analysis and a sensitivity analysis to assess the validity and reliability of the primary results.

This meta-analysis, however, was limited in some aspects as well. First, publication bias may exist in the assessment of long-term outcomes, which may be attributable to the paucity of studies. Second, although we tried our best to obtain original data to calculate the RR estimates, there were still a few crude RRs that were not adjusted by potential confounders: these might skew the conclusion. Third, the cut-points for defining an elevated PLT were not entirely consistent across studies. Fourth, the anti-platelet therapies were also not entirely consistent across included patients with or without PCI,⁴⁸ and a recent study indicated that a dosage of 150 mg/day clopidogrel might reduce major adverse cardiac and/or cerebrovascular events as compared with the currently recommended dosage of 75 mg/day clopidogrel.⁴⁹ Finally, although the trend was similar for the Caucasian studies, only 1 trial involved Asian subjects (n=279), therefore further clinical studies are warranted in that area.

Conclusion

The present meta-analyses confirmed the prognostic value of PLT in its independent association with short-term and long-term follow-up in ACS patients. A U-shaped relationship between PLT and risk estimates of adverse events has been established, but more cohort studies and research should be conducted to confirm the predictive value of thrombocytopenia at baseline.

Acknowledgments

Drs G. Xu and J. Yang contributed to conception and design of the study; Drs Christian Mueller, C. Michael Gibson contributed to conception, design and editing of the manuscript; Dr Sabina Murphy contributed to statistical analysis and editing of the manuscript; Drs Y.H. Wu and H. Wu contributed to the data acquisition, analysis, and interpretation of the data; Dr Y. Shi, critically revised the article for important intellectual content. We thank Robert Wohlhueter, who recently retired from the Centers for Disease Control and Prevention (Atlanta, GA, USA), for his invaluable support during this study and for his assistance with the manuscript. This work was supported by grants from the National Natural Science Foundation of China (Nos: 30771826, 30872140); Ministry of Science and Technology, China (No.2009DFB30390). We declare that we have no conflict of interest.

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Supplemental Files

Supplemental File 1

Figure S1. Study selection.

Figure S2. Funnel plots to test the publication bias for (A) middle platelet count (PLT) group at 1-month follow-up; (B) upper PLT group at 1-month follow-up; (C) middle PLT group at longitudinal follow-up; (D) upper PLT group at longitudinal follow-up.

Table S1. Definitions of Quality Markers

Table S2. Meta-Analysis of PLT: Requirements for Compliance With MOOSE Guideline

Please find supplemental file(s);
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