Mean platelet volume and cardiac-surgery–associated acute kidney injury: a retrospective study

Volume plaquettaire moyen et insuffisance rénale aiguë associée à la chirurgie cardiaque : une étude rétrospective

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Abstract

Purpose Increased mean platelet volume (MPV) may indicate platelet activation, platelet aggregation, and a resulting prothrombotic state. Such changes in the postoperative period have been associated with organ injury and adverse outcomes. We hypothesized that changes in MPV after cardiac surgery are associated with both a higher risk of acute kidney injury (AKI) and mortality.

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Methods In this retrospective study, we evaluated consecutive patients undergoing adult cardiac surgery patients between 12 December 2011 and 5 June 2018. The change in MPV was derived by calculating the difference between the baseline MPV before surgery and the average postoperative MPV just prior to the occurrence of AKI. We defined postoperative AKI according to Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury as either a $\geq 50\%$ increase in serum creatinine in the first ten postoperative days, or an

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increase of $\geq 0.3 \text{ mg}\cdot\text{dL}^{-1}$ during any 48-hr window across the ten-day postoperative period. Multivariable logistic regression analysis was used to examine the association between MPV change and postoperative AKI and mortality.

Results Of the 4,204 patients studied, 1,373 (32.7%) developed postoperative AKI, including 83 (2.0%) and 38 (0.9%) who developed stages II and III AKI, respectively. Compared with patients who had an increase in median postoperative MPV of 0.2 femtolitre (fL), those with an increase of 0.8 fL had an 80% increase in the odds of developing AKI (adjusted odds ratio [aOR], 1.80; 95% confidence interval [CI], 1.36 to 2.38; $P < 0.001$) and were almost twice as likely to progress to a higher severity AKI (aOR, 1.66; 95% CI, 1.28 to 2.16; $P < 0.001$). Change in MPV was not associated with mortality (aOR, 1.32; 95% CI, 0.92 to 1.89; $P = 0.14$).

Conclusion Increased MPV change in the postoperative period was associated with both increased risk and severity of AKI, but not mortality.

Résumé

Objectif Un volume plaquettaire moyen (VPM) augmenté peut être indicatif d'une activation plaquettaire, d'une agrégation plaquettaire, et de l'état prothrombotique qui en résulte. De tels changements en période postopératoire ont été associés à des lésions aux organes et à des devenir défavorables. Nous avons émis l'hypothèse que des changements du VPM après une chirurgie cardiaque seraient associés à un risque plus élevé d'insuffisance rénale aiguë et de mortalité.

Méthode Dans cette étude rétrospective, nous avons évalué des patients adultes consécutifs subissant une chirurgie cardiaque entre le 12 décembre 2011 et le 5 juin 2018. Le changement de VPM a été dérivé en calculant la différence entre le VPM de base avant la chirurgie et le VPM postopératoire moyen juste avant la survenue de l'IRA. Nous avons défini une IRA postopératoire sur la base des Directives Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury (Les maladies rénales: Guide d'exercice clinique pour améliorer les devenir globaux pour l'insuffisance rénale aiguë) en tant qu'une augmentation $\geq 50 \%$ de la créatine sérique au cours des dix premiers jours postopératoires, ou une augmentation de $\geq 0,3 \text{ mg}\cdot\text{dL}^{-1}$ pendant toute fenêtre de 48 h au cours des dix premiers jours postopératoires. Une analyse multivariée de régression logistique a été utilisée pour examiner l'association entre le changement de VPM et l'IRA postopératoire et la mortalité.

Résultats Parmi les 4204 patients à l'étude, 1373 (32,7 %) ont souffert d'IRA postopératoire, y compris 83 (2,0 %) et 38 (0,9 %) qui ont développé des IRA de stade II et III,

respectivement. Par rapport aux patients ayant manifesté une augmentation du VPM postopératoire médian de 0,2 femtolitre (fL), ceux affichant une augmentation de 0,8 fL ont démontré une augmentation de 80 % de la probabilité d'IRA (rapport de cotes ajusté [RCA], 1,80; intervalle de confiance [IC] 95 %, 1,36 à 2,38; $P < 0,001$) et couraient un risque pratiquement deux fois plus élevé de voir leur IRA progresser à un stade plus grave (RCA, 1,66; IC 95 %, 1,28 à 2,16; $P < 0,001$). Les changements de VPM n'étaient pas associés à la mortalité (RCA, 1,32; IC 95 %, 0,92 à 1,89; $P = 0,14$).

Conclusion Une augmentation accrue du VPM en période postopératoire a été associée à un risque et une gravité accrue d'IRA, mais pas à la mortalité.

Keywords acute kidney injury · cardiac surgery · platelet count · mean platelet volume · mortality

Introduction

Of the 235,000 cardiac surgical procedures performed annually in the United States,¹ approximately 30–50% of patients develop postoperative acute kidney injury (AKI), and 1–5% develop severe kidney injury requiring renal replacement therapy.^{2,3} The presence and severity of postoperative AKI have been shown to increase both hospital length of stay and rates of in-hospital mortality. Indeed, cardiac surgery patients with postoperative AKI are more likely to require intensive and supportive care and hospital readmissions, and to experience a decreased quality of life and long-term survival, compared with those without postoperative AKI.^{3–5}

The etiology of postoperative AKI after cardiac surgery is complex and multifactorial.^{2,4,5} It involves patient-related risk factors including advanced age, obesity, chronic kidney disease, diabetes mellitus, poor left ventricular function, and hypertension, as well as surgery-related factors such as ischemia-reperfusion injury, inflammatory responses, procoagulant states, and impaired regional blood flow due to low cardiac output or vasomotor dysfunction.^{3,6}

Recently, increased mean platelet volume (MPV), a routinely reported hematologic parameter of platelet size, was shown to be an indicator of platelet activation.⁷ Further, after coronary bypass grafting (CABG) surgery, MPV has been shown to be associated with late saphenous vein graft disease,⁸ postoperative atrial fibrillation,⁹ adverse postoperative cardiac events, and all-cause mortality.¹⁰ We previously reported an independent association between nadir postoperative platelet count and both AKI and short-term mortality after CABG surgery, suggesting platelet-related ischemic

complications.⁵ Indeed, in both human and animal studies, endothelial injury reliably triggers closely related hemostatic and inflammatory mechanisms, activating platelets and ultimately resulting in microvascular sludging and consequent AKI.^{11,12}

In the current study, we aimed to characterize the perioperative time course for changes in MPV, in particular how the changes related to platelet counts in a cohort of patients who underwent cardiac surgery. Our primary goal was to test the hypothesis that increased postoperative MPV after cardiac surgery is independently associated with postoperative AKI and mortality.

Methods

Study population

After approval (4 June 2018) by the Vanderbilt University Institutional Review Board, Vanderbilt University Medical Center, Nashville, Tennessee, we conducted this retrospective observational study on patients older than 18 yr who underwent cardiac surgery from 12 December 2011 to 5 June 2018. We specifically focused on the time period after 12 December 2011 when Vanderbilt University Medical Center's laboratory began measuring and reporting MPV values. From this group of 5,989 patients, we excluded 1,694 patients who had a ventricular assist device implanted or removed, surgical ablation for cardiac arrhythmias, a heart transplant, or who underwent surgery with circulatory arrest. We excluded patients with circulatory arrest given the profound impact of cardiac surgery on end-organ injury and because circulatory arrest causes hemostatic derangements that significantly increase the need for blood transfusions including platelet transfusions. The remaining 4,204 patients were included in the current study.

Data collection

The electronic medical records of all cardiac surgical patients at the Vanderbilt University Medical Center were prospectively abstracted and collected using the standardized Society of Thoracic Surgeons Adult Cardiac Surgery Database. First, we queried that database for all patients who underwent cardiac surgery at Vanderbilt University Medical Center from 12 December 2011 to 5 June 2018. Subsequently, we collected an additional set of perioperative data for these patients from two Vanderbilt University Medical Center databases: the Perioperative Data Warehouse (developed and maintained by the Vanderbilt Anesthesiology and Perioperative Informatics Research Division) and the patients' electronic medical records. Three

independent investigators (A.M.R., A.A.W., and M.D.K.) verified the data quality for completeness and consistency by performing regular cross-checks between the data that was electronically captured from the Vanderbilt databases through an automated data pull from the actual electronic health records of a selected group of study patients.

Clinical risk factors

The clinical risk factors for postoperative AKI included patient characteristics, preoperative and postoperative medication use, aortic cross-clamp time, cardiopulmonary bypass duration, blood transfusions, preoperative and postoperative serum creatinine values, platelet counts, and MPV. As per institutional protocol, preoperative antiplatelet therapy with aspirin was maintained until the day before surgery, clopidogrel was discontinued between five and seven days before surgery, direct oral anticoagulants were discontinued three days before surgery, and warfarin was discontinued four days before surgery (and bridged with intravenous heparin infusion or subcutaneous dalteparin administration as appropriate). Postoperative antiplatelet therapy with aspirin, clopidogrel, and direct oral anticoagulants was typically restarted the next day after surgery, and intravenous unfractionated heparin was also restarted the next day after surgery followed by warfarin administration if necessary.

Serum creatinine was measured preoperatively and until discharge according to institutional practice; the normal range values at the Vanderbilt Clinical Pathology Laboratory were 0.4–1.0 mg·dL⁻¹ for women and 0.6–1.3 mg·dL⁻¹ for men. Preoperative serum creatinine values were recorded up to 180 days before the index cardiac procedure on the day closest to, but not on, the day of surgery. Postoperative serum creatinine values were recorded daily for the first ten days postoperatively or until discharge, whichever came first. If any given day's serum creatinine values were not available, the last serum creatinine value measured on the previous day was carried over.

According to our institutional protocol, platelet counts and MPV were also measured preoperatively and for the first ten days postoperatively or until discharge, whichever came first, as described previously.⁵ If more than one measurement was available for platelet counts and MPV values from the same day, then the mean of these measurements was calculated and used in the subsequent analyses. The baseline MPV and platelet values were defined as the last values measured before surgery. The average postoperative MPV and platelet counts were mean values of the daily measurements before the occurrence of AKI within ten days after surgery for AKI patients, or mean values of the daily measurements during the first two

days (i.e., the median follow-up time or time to AKI for AKI patients) for non-AKI patients. The postoperative MPV and platelet count changes were calculated as the difference between baseline values and average postoperative values.

Classification of outcomes

The primary outcome of the study was postoperative AKI, ascertained and categorized according to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury, with modifications because urine output was absent.^{5,13} Using previously developed methodology, we defined postoperative AKI using preoperative (baseline) serum creatinine values that were collected up to 180 days before surgery and all available serum creatinine values that were measured for the first 10 days after surgery or until discharge, whichever came first. We diagnosed AKI using these criteria as a 50% or greater serum creatinine increase in the first ten postoperative days or $0.3 \text{ mg}\cdot\text{dL}^{-1}$ increase detected using a rolling 48-hr window across the ten-day postoperative period. We also staged postoperative AKI using KDIGO criteria as follows: stage I—risk, $> 0.3 \text{ mg}\cdot\text{dL}^{-1}$ or 1.5–1.99-fold increase from baseline values; stage II—injury, 2.0–2.99-fold increase from baseline; stage III—failure, > 3.0 -fold or greater increase from baseline within ten days or $> 4.0 \text{ mg}\cdot\text{dL}^{-1}$ or greater increase in a rolling 48-hr window.^{5,13} Patients requiring postoperative renal replacement were classified as stage III AKI.

Our secondary outcome was all-cause 30-day mortality. Survival information for the secondary outcome was ascertained from the Vanderbilt University Medical Center databases and from the Vanderbilt site-specific standardized Society of Thoracic Surgeons Adult Cardiac Surgery Database.

Statistical analysis

Patient demographics and clinical characteristics were summarized using the median [interquartile range (IQR)] for continuous variables, and percentages for categorical variables. Comparisons were made using the Wilcoxon rank sum test and the Pearson Chi square test as appropriate.

In the analysis of AKI and stage of AKI, a logistic model and a proportional odds model were used to examine the associations between changes in postoperative MPV and changes in postoperative platelet count. Postoperative AKI was a binary variable and stages of AKI were defined as an ordinal variable (no AKI, stage I, II, III), respectively, after adjusting for the clinical risk factors specified under the “clinical risk factors” section. A proportional odds model is a popular generalized linear model for modelling

the dependence of an ordinal outcome variable (postoperative AKI) on its covariates (postoperative MPV and changes in postoperative platelet count; <https://CRAN.R-project.org/package=rms>).¹⁴

In our study, we observed that patients mostly received red blood cell transfusions, and only a small number of patients received transfusion of other blood products including platelets. Therefore, in all our analyses we used “blood products administration” as a clinical variable and predictor of primary and secondary outcomes.

In the current study, any postoperative blood product administration was defined as “any blood product started after the initial surgery”. Thus, we were not able to ascertain the timing of postoperative blood product administration relative to the timing of postoperative AKI. Nevertheless, to further explore the potential confounding effect of postoperative blood product administration on the association between postoperative MPV and platelet count changes, and AKI and stages of AKI, a sensitivity analysis was performed. Postoperative blood product administration was added to the AKI/AKI stage model for adjustment. Similarly, a sensitivity analysis was performed to study the potential impact of preoperative end-stage renal disease requiring renal replacement therapy on outcomes and stages of AKI. A history of preoperative renal replacement therapy was removed from the AKI/AKI stage model.

In the analysis of 30-day mortality, given the small number of events, we selected a set of risk factors according to their clinical relevance to postoperative mortality.^{5,15} These factors included age, sex, chronic lung disease, diabetes mellitus, cerebrovascular disease, preoperative acetylsalicylic acid use, MPV (baseline), platelet count (baseline), surgery type, intraoperative and postoperative blood product administration, postoperative average MPV and platelet count change, and postoperative AKI. Similarly, the logistic regression analysis was performed to examine the associations between postoperative MPV and platelet count change with mortality.

The nonlinear effect of postoperative platelet count and MPV changes from baseline were examined using the restricted cubic spline technique with five knots. Missing values for independent variables were imputed using multiple imputation where 10 “completed” data sets were imputed, parameters were estimated using each complete data set, and the final effect estimates and their standard errors were calculated using Rubin’s rule. Adjusted odds ratios [aORs] with 95% confidence interval [CI] (and corresponding *P* value) were presented for effect size estimations. All analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided significance level of 0.05 was used for statistical inference.

Results

Demographic, clinical, and perioperative characteristics of the patients with postoperative AKI and non-AKI patients are presented in the Table. The median [IQR] age of the 4,204-patient study population was 64 [56–72] yr, and 3,008 patients (71.5%) were male. In total, 2,676 patients (64%) underwent isolated CABG surgery, 842 patients (20%) underwent isolated aortic valve or mitral valve procedures, 361 patients (9%) underwent aortic valve or mitral valve procedures with CABG surgery, and 324 patients (8%) underwent another cardiac procedure other than CABG surgery and/or valve procedures. There were several notable differences between the groups, including age, type of procedure, history of hypertension, smoking history, beta-blocker use, and intraoperative and postoperative characteristics.

The median [IQR] postoperative MPV change was 0.21 [0.03–0.40] femtolitre (fL) for AKI patients and 0.23 [0.07–0.38] fL for non-AKI patients ($P = 0.33$), and platelet count change (reduction) was $55 [25–93] \times 10^9 \cdot L^{-1}$ for AKI patients and $70 [39–106] \times 10^9 \cdot L^{-1}$ for non-AKI patients ($P < 0.001$).

Postoperative AKI

As postoperative AKI was defined as ischemic kidney injury occurring within a period of ten days after surgery, four patients who died within ten days before developing AKI were excluded. One thousand three hundred and seventy-three patients (33%) developed postoperative AKI, and 91.2% ($n = 1,252$), 6% ($n = 83$), and 2.8% ($n = 38$) of these patients met criteria for stage I, II, and III AKI, respectively. Figure 1 shows the independent associations between clinical risk factors including patient demographics, clinical and perioperative characteristics, and postoperative average MPV and platelet count changes and postoperative AKI, based on the multivariable regression analysis. The following characteristics emerged as significant risk factors for postoperative AKI: older age, black race, higher BMI, higher baseline serum creatinine concentration, higher baseline MPV values, higher baseline platelet counts, history of diabetes mellitus, cerebrovascular disease, and intraoperative blood product administration. Although there was no evidence of association between AKI status and postoperative MPV change in unadjusted comparisons (Table), both postoperative MPV and platelet count changes had significant nonlinear associations with postoperative AKI in adjusted analyses ($P = 0.007$ and $P = 0.003$, respectively). There was an “U” shape relationship between MPV change and the probability of having AKI. Compared with the median postoperative

MPV change (i.e., a 0.2 fL increase), a higher increase in postoperative MPV was associated with increased risk of AKI (Fig. 2). For example, compared with patients whose average postoperative MPV value increased by 0.2 fL (i.e., the median value) from baseline, those whose average postoperative MPV values increased by 0.8 fL from baseline (i.e., an additional 0.6-fL increment in average postoperative MPV) had an 80% increase in the odds of developing AKI (adjusted odds ratio [aOR], 1.80; 95% CI, 1.36 to 2.38; $P < 0.001$). Those whose average postoperative MPV value decreased by 0.4 fL from baseline (i.e., an additional 0.6-fL reduction in average postoperative MPV), however, had a 41% increase in odds of developing postoperative AKI (aOR, 1.41; 95% CI, 1.02 to 1.95; $P = 0.037$; Fig. 1).

For the AKI stage model, after adjusting for other demographic and clinical characteristics, patients with a postoperative MPV change greater than 0.2 fL from baseline remained at elevated odds of progressing to a higher severity of postoperative AKI (aOR, 1.66; 95% CI, 1.28 to 2.16; $P < 0.001$; Fig. 3).

In separate analyses, we explored the potential effect of postoperative blood product administration on the associations between postoperative MPV and platelet counts changes and incidence and severity of AKI. After adjusting for postoperative blood product administration, the association between postoperative MPV and platelet count changes and AKI and stages of AKI remained unchanged (available in the Electronic Supplementary Material [ESM] as eFigs 1 and 2). Further, we found that patients receiving intraoperative transfusions vs no transfusion of blood products experienced a greater median [IQR] reduction of postoperative platelets count (83 [44–125] vs 57 [31–88], respectively; $P < 0.001$). Similarly, patients who received postoperative blood transfusions had a greater postoperative platelet count reduction compared with those who did not receive postoperative blood transfusions (78 [45–121] vs 63 [33–96], respectively; $P < 0.001$).

In a subsequent sensitivity analysis, we excluded patients with a history of preoperative renal replacement therapy to explore its potential impact on the association between postoperative MPV and platelet count changes and AKI and stages of AKI. Our results remained consistent with similar effect estimates (available in the ESM as eFigs 1 and 2).

Postoperative mortality

Ninety-two of the 4,133 patients with available data (2.02%) died within 30 days of surgery (ESM eTable 1), and the causes of death are listed in ESM eTable 2. In adjusted analysis, older age, higher MPV at baseline,

Fig. 1 The estimated odds ratio of having acute kidney injury for each risk factor. The diamond shape and the horizontal segment represent the odds ratio and 95% confidence interval, respectively. All

effects were estimated from the multivariable logistic model. CABG = coronary artery bypass grafting surgery.

intraoperative and postoperative blood product administration, and postoperative AKI were significantly associated with elevated 30-day all-cause mortality (Fig. 4). Higher MPV at baseline was not significantly associated with a higher risk for 30-day all-cause mortality. In contrast, lower platelet count at baseline was associated with higher probability of 30-day all-cause mortality. The postoperative MPV change was not associated with 30-day all-cause mortality (Fig. 4). There was a significant nonlinear relationship between postoperative platelet count change and 30-day mortality (Figs 2 and 4). Compared with patients whose postoperative platelet count were unchanged, however, those who had a $100 \times 10^9 \cdot L^{-1}$ decrease had a higher odds of mortality (OR, 3.96; 95% CI, 2.26 to 6.96; $P < 0.001$; Fig. 4).

Discussion

In this single-centre retrospective observational study, we found a significant association between postoperative increase in MPV and postoperative AKI. Importantly, the magnitude of change in MPV correlated significantly with the severity of kidney injury. Postoperative increase in MPV, however, was not significantly associated with all-cause 30-day mortality.

Cardiac surgery is a major cause of acquired thrombocytopenia, predominantly due to excessive platelet consumption.¹⁶ The subsequent reactive thrombopoietic response in the postoperative period releases large numbers of immature platelets into the circulation. Because of an increase in RNA content in these platelets, they have a reticulated appearance under light microscopy, so are referred to as reticulated platelets.¹⁷

Fig. 2 Probability of having acute kidney injury (upper panels) and probability of 30-day all cause death (lower panels) conditional on postoperative mean platelet volume change and platelet count change. The blue line is probabilities calculated from the logistic models. The

shaded area in gray is the 95% confidence band. Covariates not plotted were set to their median or mode values. AKI = acute kidney injury; BL = baseline; MPV = mean platelet volume; 30-D = 30-day;

Reticulated platelets are larger, have a higher density of alpha granules, and exhibit significantly greater reactivity than mature platelets. The MPV, an automated measure of platelet size, has increasingly been associated with adverse outcomes such as acute coronary syndrome, antiplatelet drug resistance, and even inflammation.¹⁵ The results of our study show that a postoperative increase in MPV after cardiac surgery was associated with both a higher risk and severity of AKI, but there was no association between postoperative increase in MPV and mortality. This observation may indicate that once AKI develops

secondary to platelet activation after cardiac surgery, it emerges as a stronger predictor of postoperative mortality than the initial platelet activation. Alternatively, MPV may not have emerged as a predictor of mortality because of low statistical power in our smaller cohort of patients who suffered more severe stages of AKI. For example, while 1,373 patients (33%) developed AKI, 91.2% ($n = 1,252$) suffered stage I AKI whereas only 6% ($n = 83$) and 2.8% ($n = 38$) developed stages II and III, respectively. Also, in the current study, our cohort was comprised of 2,676 patients (64%) who underwent isolated CABG surgery, 842 patients

Fig. 3 The estimated odds ratio of severity (stages) of acute kidney injury for each risk factor. The diamond shape and the horizontal segment represent the odds ratio and 95% confidence interval, respectively. The odds ratios are for increase or decrease in risk for

worsening stages of acute kidney injury. All effects were estimated from the proportional odds model. CABG = coronary artery bypass grafting surgery.

(20%) who underwent isolated aortic valve- or mitral valve procedures, 361 patients (9%) who underwent aortic valve or mitral valve procedures with CABG surgery, and 324 patients (8%) who underwent another cardiac procedure other than CABG surgery and/or valve procedures. Mortality rates and predictors of mortality vary depending on the specific cardiac procedure; therefore, the effects of procedure on the relationship between MPV and mortality should be investigated, also in larger study populations with sufficient statistical power to address mortality.

The MPV values tend to be higher in conditions with acute increased platelet use and turnover, such as myocardial infarctions, unstable angina, stroke, and surgical procedures.¹⁸ Further, there is increased production of hemostatic factors and granules, higher

expression of receptors including cyclooxygenase-1, and faster responses to collagen exposure. On the other hand, in diseases with chronic inflammation, such as asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, and ulcerative colitis, MPV values are low. This is likely due to the effect of long-term cytokine exposure, including interleukin-6, on thrombopoiesis.^{19,20} In AKI specifically, platelet activation likely plays a key role in its early pathogenesis. As such, previous studies have shown an association between higher MPV values and AKI.²¹

The results of our study are consistent with those of Aydinli *et al.* who found that after CABG surgery, valvular surgery, or combined CABG and valve surgery, increased MPV predicted combined adverse events, including renal complications and 30-day mortality.²² Interestingly, they found that using MPV in conjunction with neutrophil-to-

Fig. 4 The estimated odds ratio of 30-day all-cause death for each risk factor. The diamond shape and the horizontal segment represent the odds ratio and 95% confidence interval, respectively. All effects

were estimated from the multivariable logistic model. CABG = coronary artery bypass grafting surgery.

lymphocyte ratio and red cell distribution width increased the accuracy of adverse outcomes prediction. Indeed, these observations support the mechanism for surgery-associated activation of the innate immune system, in which platelet activation plays a significant role in the early initiation of the inflammatory response reaction. The subsequent aggregation of platelets and release of platelet factors, including pro-IL-1 β , platelet-derived growth factor, and serotonin, facilitate leukocyte and neutrophil recruitment. This results in extensive inflammation, including neutrophil-mediated cytotoxicity, oxidant production, and arachidonic metabolism, which is linked to thrombosis.²³

We showed a nonlinear relationship between platelet count and MPV values. This association has been previously described,²⁴ and it has been hypothesized that the nonlinearity could be due to interactions between platelet size and thrombocytopenia.²⁵ Studies have shown

that the degree and mechanism (i.e., hypoproduction or hyperdestruction) of thrombocytopenia directly alter MPV.²¹ Patients with hyperdestruction of platelets, for example, tend to have higher MPV values and lower platelet counts. In contrast, patients with inflammatory states tend to have higher MPV values and higher platelet counts.²⁶ Indeed, in support of the latter observation, our findings showed that patients who had higher average baseline and postoperative MPV values on average had a much lower platelet count reduction (less than $100 \times 10^9 \cdot L^{-1}$) after surgery, and this was associated with a higher odds for postoperative AKI.

Risk factors for AKI

We confirmed the prognostic value of many previously identified risk factors for predicting postoperative AKI

Table Demographic and clinical characteristics of the study population, $n = 4,204$

Predictors	Number of available	Patients without AKI ($n=2,827$)	Patients with AKI ($n=1,373$)	<i>P</i> value
Demographics				
Age	4199	64 [56–71]	66 [58–73]	$<0.001^1$
Sex	4199			0.019 ²
Female		836 (30)	358 (26)	
Male		1991 (70)	1014 (74)	
Race	3974			$<0.001^2$
White		2512 (94)	1136 (88)	
African American		129 (5)	141 (11)	
Other		41 (2)	15 (1)	
Body mass index, $\text{kg}\cdot\text{m}^{-2}$	4196	28.8 [25.3–33.1]	29.9 [25.7–34.5]	$<0.001^1$
Medical history				
Chronic lung disease	4199	592 (21)	354 (26)	$<0.001^2$
Hypertension	4199	2152 (76)	1133 (83)	$<0.001^2$
Prior heart failure	4199	376 (13)	244 (18)	$<0.001^2$
Peripheral vascular disease	4199	256 (9)	181 (13)	$<0.001^2$
Diabetes mellitus	4199	1097 (39)	729 (53)	$<0.001^2$
Obstructive sleep apnea	4199	347 (12)	201 (15)	0.032 ²
Cardiovascular disease	4199	444 (16)	302 (22)	$<0.001^2$
Smoker	4198			0.001 ²
Never		1676 (59)	894 (65)	
Former		450 (16)	194 (14)	
Current		700 (25)	284 (21)	
Previous myocardial infarction	4199	1033 (37)	565 (41)	0.004 ²
Preoperative medication				
Acetylsalicylic acid	4199	2090 (74)	994 (72)	0.31 ²
Adenosine diphosphate inhibitors, 5 days before surgery	4199	673 (24)	370 (27)	0.026 ²
Amiodarone	2072	82 (6)	54 (9)	0.006 ²
Angiotensin-converting enzyme inhibitors	4199	1155 (41)	573 (42)	0.57 ²
Anticoagulants	4199	933 (33)	478 (35)	0.24 ²
Anti-platelets, 5 days before surgery	4198	70 (2)	28 (2)	0.38 ²
Beta blockers	4199	2026 (72)	1020 (74)	0.068 ²
Coumadin	4199	16 (1)	7 (1)	0.82 ²
Glycoprotein IIb/IIIa inhibitor	4199	17 (1)	0 (0)	0.004 ²
Lipid-lowering medications	4199	1878 (66)	914 (67)	0.9 ²
Intraoperative characteristics and medications				
Timing of surgery	4199			0.06 ²
Elective		1744 (62)	805 (59)	
Emergent		1083 (38)	567 (41)	
Type of surgery	4200			0.086 ²
Isolated CABG		1805 (64)	870 (63)	
Valve only		585 (21)	254 (19)	
CABG and valve		226 (8)	113 (8)	
Other		211 (7)	113 (8)	
Operative approach	4189			0.91 ²
Full conventional sternotomy		2539 (90)	1231 (90)	
Other		281 (10)	138 (10)	
Duration of cardiopulmonary bypass total, mins		71 [0–115]	66 [0–121]	0.92 ¹

Table continued

Predictors	Number of available	Patients without AKI (n=2,827)	Patients with AKI (n=1,373)	P value
Cross-clamp duration, mins		74 [56–99]	77 [56–110]	0.04 ¹
Intra-aortic balloon pump use	4199	133 (5)	86 (6)	0.033 ²
Epsilon aminocaproic acid use	4198	1509 (53)	713 (52)	0.38 ²
Tranexamic acid use	4197	21 (1)	13 (1)	0.49 ²
Intraoperative blood products administration		1011 (36)	636 (46)	<0.001 ²
Preoperative hemodynamic and laboratory tests				
Preoperative ejection fraction, %	4193	55 [50–60]	55 [45–60]	<0.001 ¹
Mean platelet volume, fL	3856	10.25 [9.70–10.85]	10.35 [9.80–11.00]	<0.001 ¹
Platelet count, 10 ⁹ L ⁻¹	3540	220 (181–266)	209 [169–257]	<0.001 ¹
Creatinine, mg·dL ⁻¹	4196	0.96 [0.83–1.14]	1.23 [0.99–1.68]	<0.001 ¹
Postoperative laboratory tests				
Average mean platelet volume, fL		10.48 [9.95–11.08]	10.60 [10.07–11.19]	<0.001 ¹
Average mean platelet volume change		0.23 [0.07–0.38]	0.21 [0.03–0.40]	0.33 ¹
Average platelet count, 10 ⁹ L ⁻¹		146 [111–182]	148 [115–186]	0.1 ¹
Average platelet count change		– 70 [– 106 to – 39]	– 55 [– 93 to – 25]	<0.001 ¹
Peak creatinine, mg·dL ⁻¹	4158	0.98 [0.84–1.15]	1.70 [1.34–2.41]	<0.001 ¹

Postoperative blood products administration

All data are represented either as median [interquartile range] or number (%). Data was analyzed with ¹Wilcoxon rank sum test or ²Pearson test with $P < 0.05$ as significant. AKI = acute kidney injury; CABG = coronary artery bypass grafting surgery; fL = femtolitre.

after cardiac surgery,⁵ including advanced age, black race, higher body mass index, higher baseline platelet counts, cardiovascular disease, and administration of intraoperative and postoperative blood products. Importantly, we observed that most of these risk factors were associated with magnitude of postoperative MPV and platelet count changes.

Advanced age, higher body mass index, and cardiovascular disease have previously been found to increase the risk for postoperative AKI.^{5,27} Patients with these risk factors often have widespread systemic vascular disease resulting in impaired renal blood flow and increased susceptibility to AKI in the perioperative period.²⁸ Given that platelets play a crucial role in the pathogenesis of most vascular disease conditions and their subsequent end-organ ischemic complications, it would be reasonable to investigate roles of antiplatelet therapy in patients at high-risk for AKI.

Our finding that higher baseline platelet counts were associated with a higher risk for postoperative AKI highlights the role of preexisting systemic inflammation and platelet activation and their potential impact on post-cardiac surgery-related acute inflammatory response reaction and higher risk for complications including AKI.²⁹ Indeed, these findings provide further support to the concept of using increased baseline platelet counts along with other inflammatory biomarkers to identify high-risk cardiac surgery patients prior to surgery who could

benefit from risk management strategies aimed at mitigating the systemic inflammatory response and platelet activation.³⁰ Of note, increased baseline MPV values indicated an elevated risk for postoperative AKI, but this association did not remain statistically significant after we adjusted for relevant clinical variables. Thus, future research is needed to investigate this complex association between preoperative MPV and platelet counts, clinical risk factors, and postoperative AKI.

Previous reports by us⁵ and others³¹ confirmed the link between intraoperative transfusion of packed red blood cells and postoperative AKI. In our current study, however, we cannot provide evidence of the causative effect of blood transfusion; the increased risk for AKI may originate from the effects of preceding anemia, preexisting kidney injury, intraoperative hypotension and volume shifts, medication use, or pathophysiologic changes triggered by the transfusion itself.³²

Risk factors for mortality

Following CABG surgery, MPV has been associated with late saphenous vein graft disease,⁸ postoperative adverse cardiac events and all-cause mortality,¹⁰ and postoperative atrial fibrillation.⁹ Whereas we found a relationship between postoperative thrombocytopenia and mortality, changes in MPV after surgery were not a significant predictor of death. This observation may reflect the

heterogeneous cohort of patients undergoing cardiac surgery with nearly one third having non-coronary cardiac procedures. While the pathophysiologic underpinning of coronary disease and atherosclerosis involves triggers and mediators of a systemic inflammatory responses leading to increased platelet reactivity and involving increased MPV (an indicator of platelet reactivity), the pathogenesis of valvular heart disease is less related to platelets.^{5,21,33,34} Furthermore, as shown in the Table, both bleeding and transfusion were significantly more common in non-CABG and in more complex procedures. Transfusion of blood products (namely platelets) and hemodilution could affect the postoperative MPV.

Limitations

Given its retrospective design, our study has several limitations. Information on some important clinical risk factors of postoperative AKI and mortality were not prospectively collected. Instead, we relied on electronic medical records and physician documentation as sources of additional information on clinical risk factors, medication use, blood transfusion, and laboratory data. Therefore, the potential effects and the magnitude of effects of certain clinical risk factors, medication use, blood transfusion, and laboratory data may have been under- or overestimated. Nevertheless, their observed predictive effects were similar to those reported from previous studies.^{5,35}

Because this study was conducted at a single tertiary academic centre, its findings may not be fully applicable to similar institutions with different mixes of cardiac surgical populations, perioperative management practices, and levels of expertise.

The reference range for normal MPV values used in our study was based on the definition set by the Vanderbilt Clinical Pathology Laboratory. This definition for a normal reference range is slightly different from other studies, and it was not specifically reported for male and female patients separately.³⁶ Furthermore, there is evidence that normal reference intervals recommended by different manufacturers of hematological analyzers could be different, and thus, laboratories often develop their own normal reference ranges.^{37,38} Therefore, we opted to use an unbiased approach of measuring and studying the effect average change of postoperative MPV values compared with baseline with AKI and mortality.

No specific protocols were used to guide intra- and postoperative transfusions or anticoagulation therapies perioperatively. Of note, there is a paucity of data on how intra- and postoperative transfusions—in particular, platelet transfusions—could influence the postoperative course of MPV and the corresponding platelet counts after

cardiac surgery. Also, as in our previous study, testing in our centre for heparin-induced thrombocytopenia was left to the discretion of the intensive care unit team.⁵ Moreover, given the retrospective design of our study, we were not able to obtain consistent data about the presence of heparin-induced thrombocytopenia or the results of laboratory screening tests for human platelet factor 4/heparin complex antibodies. According to our previous study, the incidence of heparin-induced thrombocytopenia was low (0.3%), and excluding these patients from association analyses did not change the association between postoperative thrombocytopenia and AKI.⁵

Finally, assumptions about the etiology of elevated MPV values and postoperative thrombocytopenia cannot be made. Changes in MPV values and in platelet counts have been attributed to several different acute and chronic conditions or medication use. Indeed, when it comes to the classification of platelet disorders, patients can have high, low, or normal MPV values, and high, low, or normal platelet counts.^{39,40} In the perioperative setting, increased destruction, hemodilution, and sequestration, and decreased production can all influence MPV values and platelet counts.^{5,41} As such, changes may not necessarily result in concurrent increases in MPV value and decreases in platelet counts.^{39,40} Although we previously showed a significant association between leukocyte and platelet activation and ischemic complications after cardiac surgery as a potential indication for platelet activation,⁴² we did not measure markers of inflammation and microthrombosis in our current study. Future studies will have to define and refine the context of platelet activation, changes in MPV, platelet counts, and inflammation-related ischemic complications after cardiac surgery.

In conclusion, our findings suggest an independent association between the magnitude of postoperative MPV changes and the development of postoperative AKI and severity of AKI. This complex association requires further investigation to characterize specific mechanisms that lead to postoperative AKI and mortality, and how routinely measured MPV and changes in MPV could be integrated in the perioperative patient management and decision-making about targeted therapies to reduce platelet-related ischemic complications in the setting of cardiac surgery.

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