

26. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, Hebert L, Newhouse JP, Weiler PC, Hiatt H: The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 1991; 324:377–84
27. Hellinger WC, Bacalis LP, Kay RS, Thompson ND, Xia GL, Lin Y, Khudyakov YE, Perz JF: Health care-associated hepatitis C virus infections attributed to narcotic diversion. *Ann Intern Med* 2012; 156:477–82
28. Cody SH, Nainan OV, Garfein RS, Meyers H, Bell BP, Shapiro CN, Meeks EL, Pitt H, Mouzin E, Alter MJ, Margolis HS, Vugia DJ: Hepatitis C virus transmission from an anesthesiologist to a patient. *Arch Intern Med* 2002; 162:345–50
29. Schaefer MK, Perz JF: Outbreaks of infections associated with drug diversion by US health care personnel. *Mayo Clin Proc* 2014; 89:878–87
30. Maki DG, Klein BS, McCormick RD, Alvarado CJ, Zilz MA, Stolz SM, Hassemer CA, Gould J, Liegel AR: Nosocomial *Pseudomonas pickettii* bacteremias traced to narcotic tampering. A case for selective drug screening of health care personnel. *JAMA* 1991; 265:981–6
31. Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E, Seger DL, Shu K, Federico F, Leape LL, Bates DW: Adverse drug events in ambulatory care. *N Engl J Med* 2003; 348:1556–64
32. Gerbershagen HJ, Rothaug J, Kalkman CJ, Meissner W: Determination of moderate-to-severe postoperative pain on the numeric rating scale: A cut-off point analysis applying four different methods. *Br J Anaesth* 2011; 107:619–26
33. Zalon ML: Mild, moderate, and severe pain in patients recovering from major abdominal surgery. *Pain Manag Nurs* 2014; 15:e1–12
34. Woo A, Lechner B, Fu T, Wong CS, Chiu N, Lam H, Pulenzas N, Soliman H, DeAngelis C, Chow E: Cut points for mild, moderate, and severe pain among cancer and non-cancer patients: A literature review. *Ann Palliat Med* 2015; 4:176–83
35. Poon EG, Cina JL, Churchill W, Patel N, Featherstone E, Rothschild JM, Keohane CA, Whittemore AD, Bates DW, Gandhi TK: Medication dispensing errors and potential adverse drug events before and after implementing bar code technology in the pharmacy. *Ann Intern Med* 2006; 145:426–34
36. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ: A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30:239–45
37. American College of Clinical Pharmacology response to the Institute of Medicine report “To err is human: Building a safer health system.” The Public Policy Committee. *J Clin Pharmacol* 2000;40:1075–8.
38. Battles JB, Keyes MA: Technology and patient safety: A two-edged sword. *Biomed Instrum Technol* 2002; 36:84–8
39. Sox HC Jr, Woloshin S: How many deaths are due to medical error? Getting the number right. *Eff Clin Pract* 2000; 3:277–83
40. Brennan TA: The Institute of Medicine report on medical errors—Could it do harm? *N Engl J Med* 2000; 342:1123–5
41. Incidence of adverse events and negligence in hospitalized patients. *N Engl J Med*. 1991;325:210
42. Hernández J, Vargas ML: Adverse drug events in ambulatory care. *N Engl J Med* 2003; 349:303–5; author reply 303–5
43. Bush T: Adverse drug reactions in hospitalized patients. *JAMA* 1998; 280:1742; author reply 1743–4
44. Institute of Medicine: *To Err Is Human: Building a Safer Health System*. Washington, DC, The National Academy Press, 1999

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Platelet Counts, Acute Kidney Injury, and Mortality after Coronary Artery Bypass Grafting Surgery

To the Editor:

We read with great interest the article by Dr. Kertai *et al.*,¹ in which the authors identified a novel association between postoperative nadir platelet counts and acute kidney injury (AKI) and short-term mortality after coronary artery bypass grafting surgery. Despite the elaborate statistical analysis and the innovative perspectives, we are profoundly concerned with the study design and the interpretation of statistical results, which we expect the authors to comment on and address.

First, we consider perioperative blood loss as a crucial confounding variable that should not be overlooked in the study design, nor be absent from the logistic regression analysis of AKI and mortality predictors. Significant blood loss is well established in previous literatures, poses major challenges in many cardiac surgeries, and has been identified as having strong, independent association with postoperative in-hospital mortality and AKI.^{2–5} Furthermore, the concomitant decrease in platelet counts and serum hemoglobin in this study is also a strong indicative of significant perioperative blood loss, which very much likely was the true underlying cause of both AKI and short-term mortality. Therefore, it is of crucial importance that all relevant predictors, especially such important predictor as perioperative blood loss, be included in the logistic regression analysis. However, according to the authors, they were not able to investigate the influence of postoperative bleeding due to the retrospective nature of the study, which we readers hesitate to give our full trust given the requirements of comprehensive intensive monitoring postcardiac surgeries. Hence, before the effect of perioperative blood loss on AKI is conclusively affirmed, we readers should be highly cautious about the conclusions this study attempted to present, *i.e.*, the novel association between thrombocytopenia and postoperative AKI. Such conclusions may be distracting, if not misleading, to us readers, since the association between perioperative blood loss and AKI may be concealed behind the seemingly causative thrombocytopenia. We, therefore, suggest that the authors and interested readers focus more attention on perioperative blood loss, rather than platelet reduction, in the future researches of postoperative AKI.

Second, previous studies have verified that coagulation factor and fibrin dysfunctions are also in significant association with postoperative kidney and myocardial injuries.^{6,7} Therefore, we advise the authors to explore the functions of the whole set of serum coagulant components on AKI from a broader view, other than focusing on the single variable of platelet count.

In summary, we applaud Dr. Kertai *et al.* for their enlightening study and opinions on AKI and short-term mortality after cardiac surgeries. However, it is of utmost importance for us readers to keep alerted of the conclusions this study intended to present, in order to avoid overreliance on the statistical results while neglecting the possible biologic implausibility. We expect the authors to further address and explore on the above issues.

Competing Interests

The authors declare no competing interests.

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References

1. Kertai MD, Zhou S, Karhausen JA, Cooter M, Jooste E, Li YJ, White WD, Aronson S, Podgoreanu MV, Gaca J, Welsby IJ, Levy JH, Stafford-Smith M, Mathew JP, Fontes ML: Platelet counts, acute kidney injury, and mortality after coronary artery bypass grafting surgery. *ANESTHESIOLOGY* 2016; 124:339–52
2. Karkouti K, Wijeyesundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA, Ghannam M, Yeo E, Djaiani G, Karski J: The independent association of massive blood loss with mortality in cardiac surgery. *Transfusion* 2004; 44:1453–62
3. Goren O, Matot I: Perioperative acute kidney injury. *Br J Anaesth.* 2015; 115(suppl 2):ii3–14
4. Walsh M, Garg AX, Devereaux PJ, Argalious M, Honar H, Sessler DI: The association between perioperative hemoglobin and acute kidney injury in patients having noncardiac surgery. *Anesth Analg* 2013; 117:924–31
5. Brienza N, Giglio MT, Marucci M, Fiore T: Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit Care Med* 2009; 37:2079–90
6. Mörtberg J, Blombäck M, Wallén H, He S, Jacobson SH, Spaak J: Increased fibrin formation and impaired fibrinolytic capacity in severe chronic kidney disease. *Blood Coagul Fibrinolysis* 2016; 27:401–7
7. Campo G, Valgimigli M, Ferraresi P, Malagutti P, Baroni M, Arcozzi C, Gemmati D, Percoco G, Parrinello G, Ferrari R, Bernardi F: Tissue factor and coagulation factor VII levels during acute myocardial infarction: Association with genotype and adverse events. *Arterioscler Thromb Vasc Biol* 2006; 26:2800–6

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In Reply:

We appreciate comments from Drs. Hui and Yu regarding our published article titled “Platelet Counts, Acute Kidney Injury, and Mortality after Coronary Artery Bypass Grafting Surgery.”¹ The letter indicated that “despite the elaborate statistical analysis and the innovative perspectives,” they were concerned over “the study design and the interpretation of statistical results” of our study. More specifically, the letter highlighted that information on perioperative blood loss was not included in the logistic regression analysis and

“suggest focusing more attention on perioperative blood loss, rather than platelets reduction in future research studies on postoperative acute kidney injury.” In support of their statement, Drs. Hui and Yu critiqued that significant blood loss is an independent risk factor for postoperative acute kidney injury (AKI) and in-hospital mortality after cardiac surgery. However, all studies cited in support of their statement did not directly test blood loss as a predictor of AKI. For example, one study defined significant blood loss as a need for large volume of blood transfusion (administration of more than or equal to 5 units of packed erythrocytes within 1 day of surgery)²; another reviewed risk factors and management of AKI without discussing the role of blood loss for predicting perioperative AKI³; another study was conducted in patients undergoing non-cardiac surgery and investigated the role of perioperative hemoglobin as a predictor of AKI⁴; and the last citation was a meta-analysis of studies about the effects of perioperative hemodynamic optimization for postoperative renal dysfunction.⁵ Although several studies have found transfusion and anemia to be associated with AKI in cardiac surgery, none have addressed blood loss itself as a predictor.^{6–8} Further, the incidence of major bleeding requiring reoperation after elective coronary artery bypass grafting surgery is reported to be around 2.1%,⁹ and therefore given this low incidence, it is unlikely that major bleeding and/or blood loss accounted for a higher risk for AKI in our study. In addition, accurate measurement of blood loss intraoperatively in cardiac surgery with the use of cardiopulmonary bypass has limitations. Similarly, chest tube outputs after surgery is not a reliable method of capturing blood loss because the hemoglobin content in the chest tube is not measured.

Drs. Hui and Yu also alluded that our study did not explore the functions of the whole set of serum coagulant components on AKI from a “broader view, other than focusing on the single variable of platelet count.” Again, in support of their statement, they reference two studies conducted in nonsurgical populations—one on increased fibrin formation and impaired fibrinolysis capacity in severe chronic kidney disease¹⁰ and the other on the role of tissue factor and coagulation factor VII levels in patients with acute myocardial infarction.¹¹ We are not aware of any studies to date to indicate that increased fibrin formation, impaired fibrinolysis capacity, tissue factor, or coagulation factor VII levels play a significant role in the development of postoperative AKI after cardiac surgery. Further, many of these factors of coagulation are not routinely measured during and after cardiopulmonary bypass in patients undergoing cardiac surgery. On the contrary, previous studies indicated that contact activation during and after cardiopulmonary bypass can lead to formation of circulating microaggregates (adhesions among leukocytes, activated platelets, and endothelial cells), and along with persistent thrombin generation, microaggregates may