Correspondence

Reply to “Is mean platelet volume a prognostic marker for hemodialysis patients?”

Steven Kim a,1, Kamyar Kalantar-Zadeh b,1, Connie M. Rhee b,a,1

a Department of Mathematics and Statistics, California State University Monterey Bay, 100 Campus Center, Seaside, CA 93955, United States
b Harold Simmons Center for Chronic Disease Research and Epidemiology, University of California Irvine, 101 The City Drive South, Suite 400, Orange, CA, United States

We appreciate the comments from Drs. Zeng, Jiang, and Wang [1] regarding our original research study, “Mean Platelet Volume and Mortality Risk in an Incident Hemodialysis Cohort” [2]. In response to their first point, we agree that, given the observational study design, our findings of an association between incrementally higher mean platelet volume (MPV) levels and increasingly higher mortality risk may not have a causal interpretation, and due to data limitations, some confounders (e.g., certain comorbidities and medications) could not be accounted for. However, it should be noted that our study is the first to examine longitudinal MPV levels and mortality in a US-based nationally representative cohort of hemodialysis patients on a large unprecedented scale, with the objective of motivating future studies that will confirm associations, explore underlying mechanisms, and determine whether MPV-related death risk is modifiable with therapeutic interventions. In addition, the availability of detailed and granular patient-level data in our study allowed us to account for many key confounders such as markers of inflammation and nutrition (e.g., serum albumin as a negative acute phase reactant and nutritional index, normalized protein catabolic rate as a marker of protein intake, and serum creatinine as a proxy of muscle mass [3]) in sensitivity analyses. Notably, among the various medications that may modify MPV levels that are relevant to the hemodialysis population, we observed robust associations between high MPV level and mortality across strata of erythropoietin stimulating agent use [4–6].

The authors also highlighted concerns about missed opportunity to gain insight into mechanistic pathways underlying the high MPV—mortality association given the lack of cause-specific mortality data. However, given that cause-of-death is typically non-adjudicated in clinical data sources (i.e., collected as a part of routine patient care as opposed to research purposes), there may be a tendency towards an over-reporting of cardiovascular deaths and subsequent outcome misclassification [7,8]. Thus, we selected all-cause mortality as a more robust outcome of interest in our study.

Finally, in response to concerns about heterogeneous methodologic approaches used across various hospitals and centers that may influence MPV levels, all laboratory data were collected in the ambulatory setting and were measured in a single laboratory using uniform techniques, reducing the likelihood of measurement bias. Furthermore, any resultant misclassification of MPV levels would likely be non-differential, rendering our findings conservative.

Given that routinely-used hematologic indices such as platelet count may be inadequate metrics of thrombotic vs. bleeding propensity in dialysis patients, MPV has appeal as a widely-available, simple, and economical marker for assessing platelet reactivity [9]. However, further studies are needed to confirm findings, and well-designed interventional studies that lower MPV levels may provide insight into the causal implications of MPV upon the cardiovascular health and survival of dialysis patients.

Funding/support and role of funder/sponsor

This work was supported by the National Institutes of Health/National Institutes of Diabetes and Digestive and Kidney Diseases (K23-DK102903 to CMR, R01DK09568 to KKZ) and philanthropist grants from Mr. Harold Simmons, Mr. Louis Chang, and Dr. Joseph Lee. The funder/sponsor had no role in the study design; collection, analysis, and interpretation of the data; in writing the report; and in the decision to submit the article for publication.

Conflicts of interest and financial disclosures

None of the authors declare any relevant conflicts of interest.

References

[1] D. Zeng, J. Jiang, C. Wang, Is mean platelet volume a prognostic marker for hemodialysis patients? Int. J. Cardiol. 229 (2017) 44.
[2] S. Kim, M.Z. Molnar, G.C. Fonarow, E. Streja, J. Wang, D.L. Gillen, et al., Mean platelet volume and mortality risk in a national incident hemodialysis cohort, Int. J. Cardiol. 220 (2016) 862–870.
[3] J.J. Carrero, J. Chen, C.P. Kovesdy, K. Kalantar-Zadeh, Critical appraisal of biomarkers of dietary intake and nutritional status in patients undergoing dialysis, Semin. Dial. 27 (6) (2014) 586–589.
[4] M. Diaz-Ricart, E. Etebanell, A. Cases, J. Lopez-Pedret, R. Castillo, A. Ordinas, et al., Erythropoietin improves signaling through tyrosine phosphorylation in platelets from uremic patients, Thromb. Haemost. 82 (4) (1999) 1312–1317.
Correspondence

[5] C. van Geet, D. Hauglustaine, L. Verresen, M. Vanrusselt, J. Vermylen, Haemostatic effects of recombinant human erythropoietin in chronic haemodialysis patients, Thromb. Haemost. 61 (1) (1989) 117–121.

[6] X.J. Zhou, N.D. Vaziri, Defective calcium signalling in uraemic platelets and its amelioration with long-term erythropoietin therapy, Nephrol. Dial. Transplant. 17 (6) (2002) 992–997.

[7] S.A. Coady, P.D. Sorlie, L.S. Cooper, A.R. Folsom, W.D. Rosamond, D.E. Conwill, Validation of death certificate diagnosis for coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study, J. Clin. Epidemiol. 54 (1) (2001) 40–50.

[8] D.R. Lakireddy, M.S. Gowda, C.W. Murray, K.R. Basarakodu, J.L. Vacek, Death certificate completion: how well are physicians trained and are cardiovascular causes overstated? Ann. J. Med. 117 (7) (2004) 492–498.

[9] S.G. Chu, R.C. Becker, P.B. Berger, D.L. Bhatt, J.W. Eikelboom, B. Konkle, et al., Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis, J. Thromb. Haemost. 8 (1) (2010) 148–156.