Response to Letters to the Editor RE: Association of Vitamin D Status and COVID-19-Related Hospitalization and Mortality

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M. Speeckaert et al. correctly point out the potential role that DBP polymorphisms may exert on COVID-19 not only because of effects on bioavailable 25(OH)D levels but also due to other actions of DBP independent of binding to vitamin D metabolites.[1] Because DBP is not routinely measured in clinical practice however, we were not able to ascertain the contribution of DBP or DBP polymorphisms on COVID-related outcomes in this study.[2]

DBP and serum albumin (which also binds 25(OH)D, albeit to a lesser extent than DBP), act as negative acute phase response proteins. Thus, serum albumin and DBP can be lower in acute or chronic disease, resulting in potentially lower serum 25(OH)D levels during acute infection with COVID-19.[3] To mitigate this concern, we excluded patients with 25(OH)D tests performed within 14 days of a positive SARS-CoV-2 test.[4] Serum albumin is routinely measured in clinical practice and can serve as a marker for vitamin D binding capacity. Thus, adjusting for serum albumin levels in studies of 25(OH)D can partially account for the contribution of vitamin D binding capacity on study outcomes. When we included serum albumin as a covariate in multivariable models however, we found no impact on our results that still showed an independent protective effect of higher 25(OH)D levels on COVID-19 adverse outcomes, hospitalization, and mortality.[2] In addition, the interaction between 25(OH)D and serum albumin was not significant.

The commentary by H Shafeeq Ahmed questions the generalizability of the study's findings as the data are derived from a sample of veterans enrolled in the VA healthcare system. The author is correct that veterans are disproportionately male and older, and have multiple comorbidities. The VA healthcare system is the largest and most diverse healthcare system in the USA and our sample contained a total of 4,599 patients, one of the largest to investigate the independent contribution of 25(OH)D levels on COVID-related outcomes. Because of the VA's national electronic health record, we had sufficient numbers of women and younger veterans to conduct multivariable analyses to adjust for potential confounding of male sex and older age on COVID-19-related adverse outcomes. We also adjusted for multiple medical comorbidities (i.e., obesity, diabetes, cardiovascular disease, etc.) all of which could explain worse COVID-related outcomes in this sample. We still found an independent effect of lower 25(OH)D levels associated with COVID-related hospitalization and mortality, and the converse—that higher 25(OH)D levels were associated with more favorable clinical outcomes.[2]

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Declarations:

Conflict of Interest: *None of the authors have any conflicts of interest to report*

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