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# Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North—supports vitamin D as a factor determining severity. Authors' reply

We read with interest the comments by Rhodes et al, and Panarese and Shahini, regarding a potential association between vitamin D levels and risk of severe coronavirus-19 disease (COVID-19).[1,2] Their cogent arguments regarding low dose vitamin D supplementation during a period of lockdown, particularly in areas of low sunlight exposure and low baseline vitamin D levels, appear reasonable in the context of bone protection. However, whether this association carries forward to a protective effect against severe COVID-19 remains tenuous, and best regarded with caution.

Vitamin D has been associated with multiple cellular processes implicated in innate and adaptive immunity,[3] and multiple disease associations with vitamin D deficiency have been noted.[4] However, despite more than a decade of interventional clinical studies, few have supported vitamin D supplementation for altering clinical outcomes for patients with inflammatory disease.[5] Variable study methodology, including dose and method of vitamin D administration, or target 25-hydroxy vitamin D levels, may have contributed to the many negative studies to date. However, it is more likely that laboratory data and clinical associations have failed to translate to causality or meaningful therapy.[6]

The data regarding north-south gradient and outcomes of COVID-19 outlined by Panarese and Shahini, and Rhodes et al must be interpreted in the context of public health measures, population density, urban connectivity and spread of COVID-19 across various countries. Strict physical distancing and shutdown measures were implemented much earlier in Australia (where a large proportion of the population lives in a latitude below 32 degrees south), New Zealand and Norway, accounting for improved outcomes. In comparison, countries with relatively high sunlight exposure such as Indonesia, Morocco and Egypt, are currently experiencing high case-fatality rates (CFRs).[7] Singapore, which acted swiftly, is currently experiencing a surge in cases.

Different practices in testing for the virus and in reporting medical outcomes will also skew comparison of mortality figures between nations. Furthermore, until cross-sectional antibody testing has been performed, CFRs will exclude undiagnosed asymptomatic patients and are likely to be gross overestimates that should be interpreted with care.

Apart from physical distancing and shutdown measures after identification of the first few cases of COVID-19, there are likely to be multiple confounders to any potential relationship between vitamin D and severe outcomes from vitamin D. Age of population is the strongest determinant of severe outcomes.[8,9] The median age of the population tends to be substantially higher in countries with higher than lower CFRs.[10]

It may be premature to suggest widespread vitamin D supplementation with the aim to improve outcomes from COVID-19. It would be reasonable, however, to consider vitamin D supplementation to protect musculoskeletal health in those at risk of deficiency due to being housebound, as recommended currently by the UK National Health Service (NHS online). Additionally, measured recommendations for a balanced nutritious diet, physically distanced exercise and sunlight exposure may be better for overall physical and mental health during this global crisis.

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## LINKED CONTENT

This article is linked to Al-Ani et al and Rhodes et al papers. To view these articles, visit https://doi.org/10.1111/apt.15779 and https://doi.org/10.1111/apt.15777.

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# Editorial: hepatitis B DNA thresholds and risk of hepatocellular carcinoma: different number patterns in HBeAg-positive versus HBeAg-negative patients

The classical REVEAL studies demonstrated that serum HBV DNA concentrations are significantly associated with an increased incidence of hepatocellular carcinoma (HCC).[1,2] In the latter study, the risk of incident HCC was linearly related to serum HBV DNA at study entry but was highest for serum HBV DNA concentrations >$10^6$ copies/mL. The effect of higher HBV DNA concentrations than this was not analysed. Kim et al have analysed HCC risk at different HBV DNA thresholds in 6949 Korean HBeAg-positive and HBeAg-negative patients without cirrhosis at baseline, and low or mildly elevated serum ALT.[3] The mean age of the cohort was 45 years; the median ALT level was 25 U/L. After 8 years of median follow-up, 5.2% developed HCC.

In the HBeAg-negative patients serum HBV DNA concentrations were linearly associated with HCC risk. Patients with HBV DNA >5 $\log_{10}$ IU/mL showed the highest risk. However among the HBeAg-positive patients, HCC risk was highest in those with serum DNA >6-7 $\log_{10}$ IU/mL, but unexpectedly, lowest in those with higher levels (>8 $\log_{10}$ IU/mL). ALT concentrations were not an independent predictor of HCC risk. The results in the HBeAg-positive and negative groups should be viewed separately as 41 per cent of the HBeAg-positive patients had serum HBV DNA >8 $\log_{10}$ IU/mL, vs only 3 (0.1%) of the HBeAg-negative patients.

What the authors termed medium levels of serum hepatitis B DNA are actually relatively high levels of HBV replication. The authors point out that very high concentrations of HBV DNA and persistently normal ALT are criteria for the "immune tolerance phase" in HBeAg-positive patients but acknowledge the controversy. Immunological tolerance may be a constituent of neonatal hepatitis B infection and subsequent chronicity, but we should be wary of imprecise definitions of immunologic tolerance and response defined only by the replicative state of hepatitis B and serum ALT at later, different phases of the disease, without precise experimental observations of the host immune response.[4]

Their finding that HCC risk was lowest in the cohort with HBV DNA >8 $\log_{10}$ IU/mL nonetheless requires explanation. Patients with serum HBV DNA concentrations set at these very high levels may not exhibit severe hepatic necro-inflammation. However, patients with somewhat lower HBV DNA concentrations may be unveiling and traversing a biological gradient of decreasing HBV DNA concentrations, transitioning across a different stage of the natural history (and host immune phenotype), selection of HBeAg-minus variants, accumulating hepatocyte damage and an alteration in hepatocyte turnover and indeed hepatitis B virus integrations in the host genome that could presage clonal change.[5]

The data raise the important question of extension of treatment to chronically infected patients with replicative hepatitis B, regardless of serum ALT levels in both HBeAg-positive and negative patients. It will be difficult to conclude the requisite long-term controlled prospective studies to validate treatment. Nonetheless the inference is that therapy should not be delayed for young adults with replicative hepatitis B and normal or only "mild" ALT elevations. The