TABLE 1 (Continued)

Countries	Latitude degrees	Total cases (N)	Total deaths, N (%)	Deaths/1 Million population, N
Nigeria	10	174	2 (1.1)	0.02
Costa Rica	10	375	2 (0.5)	0.4
Ghana	8	195	5 (2.6)	0.2
Panama	8	1317	32 (2.4)	11
Venezuela	8	144	3 (2.0)	0.2
Ivory Coast	8	190	1 (0.5)	0.1
Sri Lanka	7	148	3 (2.0)	0.2
Cameroon	5	255	6 (2.3)	0.3
Malaysia	5	3116	50 (1.6)	2
Brunei	4	133	1 (0.7)	2
Colombia	3	1065	17 (1.7)	0.7
Singapore	1	1000	4 (0.4)	1
Ecuador	−1	2758	98 (3.5)	10
Indonesia	−2	1790	170 (9.5)	0.7
DRC	−4	123	11 (8.9)	0.2
Peru	−7	1323	47 (3.6)	3
Mayotte	−13	116	1 (0.9)	7
Bolivia	−17	123	7 (5.7)	0.9
Mauritius	−20	161	7 (4.3)	6
Australia	−25	5137	25 (0.5)	1
Southern Hemisphere				
South Africa	−29	1380	5 (0.4)	0.2
Chile	−31	3031	16 (0.5)	2
Argentina	−34	1133	33 (2.9)	1
Uruguay	−34	350	2 (0.6)	1
New Zealand	−41	797	1 (0.1)	0.1

Note: Data extracted from https://www.worldometers.info/coronavirus/ (Accessed April 2, 2020).

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REFERENCES

1. Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. [published online ahead of print, 2020 Mar 29]. *Aliment Pharmacol Ther.* 2020;51:843-851.
2. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. [published online ahead of print, 2020 Mar 3]. *Gastroenterology.* 2020. S0016–5085(20)30282–1.
3. Panarese A, Pesce F, Porcelli P, et al. Chronic functional constipation is strongly linked to vitamin D deficiency. *World J Gastroenterol.* 2019;25:1729-1740.
4. Zhang Y, Leung DYM, Richers BN, et al. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. *J Immunol.* 2012;188:2127-2135.
5. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. *Nutrients.* 2015;7:4240-4270.
6. Zdrenghea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation of innate immune responses to respiratory viral infections. *Rev Med Virol.* 2017;27. https://doi.org/10.1002/rmv.1909
7. Arboleda JF, Fernandez GJ, Urcuqui-Inchima S. Vitamin D-mediated attenuation of miR-155 in human macrophages infected with dengue virus: Implications for the cytokine response. *Infect Genet Evol.* 2019;69:12-21.
8. Kong J, Zhu X, Shi Y, et al. VDR attenuates acute lung injury by blocking Ang-2-Tie-2 pathway and renin-angiotensin system. *Mol Endocrinol.* 2013;27:2116-2125.
9. Tsujino I, Ushikoshi-Nakayama R, Yamazakj T, et al. Pulmonary activation of vitamin D3 and preventive effect against interstitial pneumonia. *J Clin Biochem Nutr.* 2019;65:245-251.
10. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ.* 2017;356:i6583.

Letter: Covid-19, and vitamin D. Authors' reply

EDITORS,

We read with great interest the letter from Drs Panarese and Shahini, regarding our review article. We are glad that our review has helped Italian colleagues in this pandemic and grateful for their comments.

Interestingly, they found that northerly latitude is associated with increased mortality rate and hospitalisation rate for COVID-19 worldwide.[1] One possible explanation was the vitamin D deficiency due to low ultraviolet exposure in Northern countries and now probably compounded by "shut-down" measures, as mentioned by Drs Panarese and Shahini. It has also been suggested that weather conditions of low temperature and relative humidity might allow the virus to survive longer outside the body than under warmer conditions.

A recent review that also supported the possibility of vitamin D reducing the risk of COVID-19 infections and deaths documented the various relevant actions of vitamin D.[2] These include maintenance of cell junctions, strengthening cellular immunity by reducing the cytokine storm with impacts on tumour necrosis factor α and interferon γ,[2] and modulating adaptive immunity through suppressing T helper cell type 1 (Th1) responses and promoting induction of T regulatory cells.[3] Vitamin D supplementation increases the $CD4^+$ T cell count in

HIV infection,[4] and one of the main manifestations of severe SARS-CoV-2 infection was lymphopenia. Vitamin D deficiency can therefore be implicated in ARDS, and heart failure as well as sepsis,[2] and these can all be manifestations of critically ill COVID-19 patients.

It is also important that vitamin D is involved in two other critical regulatory systems. Thus hypovitaminosis D promotes the renin-angiotensin system (RAS), chronic activation of which may lead to chronic cardiovascular disease (CVD) and decreased lung function.[5] Patients with these comorbidities account for a higher proportion of critically ill cases in COVID-19. Recently Hanff et al[6] speculated that CVD or RAS blockade drugs might augment ACE2 levels, increasing available substrate for SARS-CoV-2 infection. SARS-CoV-2 infection is thought to downregulate ACE2 function, leading to toxic Angiotensin II overaccumulation which in turn may contribute to ARDS or fulminant myocarditis. Another prominent feature of severe COVID-19 is coagulopathy. A higher level of D-dimer was found in ICU patients than non-ICU patients,[7] indicating a predominantly pro-thrombotic DIC. It was confirmed in pathology that microvascular thrombosis was found in lung tissues of COVID-19.[8] Vitamin D deficiency has also been reported to correlate with increased risk for thrombosis, and vitamin D controls the expression of several genes relevant to cellular proliferation, differentiation, apoptosis, and angiogenesis.[9]

Therefore, together with Drs Panarese and Shahini, we agree that vitamin D deficiency may well be associated with an increased risk of severity in COVID-19. Further study of the impact of vitamin D levels on outcome in hospitalised patients is urgently needed. Meanwhile, it seems highly plausible that appropriate supplementation of vitamin D, as already recommended for populations with high prevalence of vitamin D deficiency, may reduce the risk of severe COVID-19 outcomes.

The authors' declarations of personal and financial interests are unchanged from those in the original article.[10]

LINKED CONTENT

This article is linked to Sands et al papers. To view these articles, visit https://doi.org/10.1111/apt.15555 and https://doi.org/10.1111/apt.15716.

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REFERENCES

1. Panarese A, Shahini E. Letter: Covid-19, and vitamin D. *Aliment Pharmacol Ther*. 2020;51:996-998.
2. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients*. 2020;12(4):988.
3. Cantorna MT, Snyder L, Lin YD, Yang L. Vitamin D and 1,25(OH)2D regulation of T cells. *Nutrients*. 2015;7(4):3011-3021.
4. Alvarez N, Aguilar-Jimenez W, Rugeles MT. The potential protective role of vitamin D supplementation on HIV-1 infection. *Front Immunol*. 2019;10:2291.
5. Shi Y, Liu T, Yao LI, et al. Chronic vitamin D deficiency induces lung fibrosis through activation of the renin-angiotensin system. *Sci Rep*. 2017;7(1):3312.
6. Hanff TC, Harhay MO, Brown TS, Cohen JB, Mohareb AM. Is there an association between COVID-19 mortality and the renin-angiotensin system – a call for epidemiologic investigations. *Clin Infect Dis*. 2020.
7. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061.
8. Yao XH, Li TY, He ZC, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. *Zhonghua Bing Li Xue Za Zhi*. 2020;49(0):E009. (in Chinese)
9. Mohammad S, Mishra A, Ashraf MZ. Emerging role of vitamin D and its associated molecules in pathways related to pathogenesis of thrombosis. *Biomolecules*. 2019;9(11):649.
10. Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Aliment Pharmacol Ther*. 2020;51(9):843-851.

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Letter: corticosteroid use alongside tofacitinib in OCTAVE Open

Editors,

We read with great interest the study by Sands *et al*.[1] The authors found that flexible dosing with tofacitinib 5 mg b.d. and tofacitinib 10 mg b.d. can be incorporated into long-term disease management strategies for patients with ulcerative colitis (UC). This study is important and interesting; however, one weakness of this study is the lack of information about whether glucocorticoid withdrawal was considered as a key secondary