

Letter: Covid-19, and vitamin D

EDITORS,

We read with interest the article by Tian Y et al reviewing the gastrointestinal aspects of the novel coronavirus disease (Covid-19).¹ As digestive endoscopists, we have adopted personal protective equipment in the endoscopy setting. Moreover, considering the importance of viral persistence in stools, we agree with the incorporation of rectal swab testing before discharging patients for identification of potential Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) positivity.

Angiotensin converting enzyme 2 (ACE2) is the host receptor for SARS-CoV-2 entry into intestinal and alveolar cells.² Subsequent dysregulation of the renin-angiotensin system may lead to massive cytokine activation resulting in potentially fatal acute respiratory distress syndrome (ARDS). Covid-19 has a mortality rate that is currently higher in Northern latitudes, with Italy the highest (11.9%). Deaths and hospitalisations have to date occurred in 5.2% and 22% of patients in Northern latitudes, in 3.1% and 9.5% close to the Equator, in 0.7% and 8.7% in Southern latitudes, respectively (Table 1). Therefore, Covid-19 outbreaks and particularly mortality exhibit a decreasing North-South gradient.

One explanation of this North-South gradient might be the high prevalence of older people in Northern European populations, predisposing to a higher probability of cardio-pulmonary and metabolic co-morbidities. Another possibility might be vitamin D deficiency which may also contribute to airway/gastrointestinal infectious illnesses.³ Elderly Italians display a very high prevalence of hypovitaminosis D, especially during the winter.³

Vitamin D has immuno-modulatory properties, that include downregulation of pro-inflammatory cytokines,³⁻⁷ and has been shown to attenuate lipopolysaccharide-induced acute lung injury in mice by blocking effects on the angiotensin (Ang)-2-Tie-2 signalling pathway and on the renin-angiotensin pathway.⁸ Tsujino I et al have recently shown, both in a mouse model of bleomycin-induced interstitial pneumonia and in human cell lines, that vitamin D3 is locally activated in lung tissue and has a preventive effect on experimental interstitial pneumonitis.⁹ Although it is more likely that any protective effect of vitamin D against Covid19 is related to suppression of cytokine response and

reduced severity/risk for ARDS, there is also evidence from a meta-analysis that regular oral vitamin D2/D3 intake (in doses up to 2000 IU/d without additional bolus), is safe and protective against acute respiratory tract infection, especially in subjects with vitamin D deficiency.¹⁰



It therefore seems plausible that Vitamin D prophylaxis (without over-dosing) may contribute to reducing the severity of illness caused by SARS-CoV-2, particularly in settings where hypovitaminosis D is frequent. This will include people currently living in Northern countries and those with underlying gastroenterological conditions where vitamin D deficiency is more prevalent. This may become even more important with absence of sunlight exposure as a consequence of "shut-down" measures to control the spread of Covid19. For this to be effectively implemented will require worldwide government guidelines, and further studies looking at possible impacts of vitamin D deficiency on Covid-19 outcomes are urgently needed.

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Declaration of personal interests: We thank everyone who is working to resolve the SARS-CoV-2 pandemic.

LINKED CONTENT

This article is linked to Tian et al and Tian and Rong papers. To view these articles, visit <https://doi.org/10.1111/apt.15731> and <https://doi.org/10.1111/apt.15764>.

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TABLE 1 Worldwide mortality rate of COVID-19 pandemic, according to geographical distribution in 108 countries. Includes countries with at least 100 cases

Countries	Latitude degrees	Total cases (N)	Total deaths, N (%)	Deaths/1 Million population, N
Northern Hemisphere				
Russia	65	3548	30 (0.8)	0.3
Iceland	65	1220	2 (0.2)	12
Norway	64	4898	45 (0.9)	13
Finland	63	1518	17 (1.1)	5
Canada	61	9731	129 (1.3)	7
Sweden	59	4947	239 (4.8)	40
Estonia	59	858	11 (1.3)	11
Denmark	56	3355	104 (3.1)	31
UK	55	29 474	2352 (8.0)	73
Lithuania	55	649	8 (1.2)	5
Belarus	55	163	2 (1.2)	0.8
Ireland	53	3447	85 (2.5)	32
Netherlands	52	13 614	1173 (8.6)	103
Poland	52	2633	45 (1.7)	2
Germany	51	78 115	944 (1.2)	19
Belgium	50	15 348	1011 (6.6)	125
Luxembourg	50	2319	29 (1.2)	58
Czechia	50	3604	40 (1.1)	6
Ukraine	49	804	20 (2.5)	0.8
UAE	49	814	8 (1.0)	1
Slovakia	49	426	1 (0.2)	0.2
Hungary	47	585	21 (3.6)	4
Switzerland	47	18 117	505 (2.8)	83
Austria	47	10 877	158 (1.4)	23
Moldova	47	423	5 (1.2)	4
Kazakhstan	47	402	3 (0.7)	0.3
France	46	56 989	4032 (7.1)	116
Romania	46	2738	94 (3.4)	8
Slovenia	46	897	16 (1.8)	13
Croatia	45	963	6 (0.6)	4
San Marino	44	236	28 (11.9)	943
Bosnia and Herzegovina	44	512	15 (2.9)	7
Serbia	44	1060	28 (2.6)	6
Montenegro	43	140	2 (1.4)	3
Italy	42	110 574	13 155 (11.9)	263
Andorra	42	390	14 (3.6)	233
Bulgaria	42	449	10 (2.2)	3
Albania	41	277	16 (5.8)	7
North Macedonia	41	354	11 (3.1)	9
Azerbaijan	41	400	5 (1.2)	0.7

(Continues)

TABLE 1 (Continued)

Countries	Latitude degrees	Total cases (N)	Total deaths, N (%)	Deaths/1 Million population, N
Uzbekistan	41	190	2 (1.0)	0.006
Armenia	41	663	4 (0.6)	2
USA	40	215 357	5113 (2.4)	29
Portugal	40	8251	187 (2.3)	29
Spain	39	110 238	10 003 (9.1)	266
Greece	39	1415	51 (3.6)	7
Turkey	39	15 679	277 (1.8)	7
Japan	36	2384	57 (2.4)	0.6
S. Korea	36	9976	169 (1.7)	4
Diamond Princess	36	712	11 (1.5)	n.a.
China	35	81 589	3318 (4.1)	2
Cyprus	35	320	9 (2.8)	7
Lebanon	34	494	16 (3.2)	3
Tunisia	34	423	12 (2.8)	2
Afghanistan	34	239	4 (1.7)	0.2
Iraq	33	728	52 (7.1)	2
Iran	33	50 468	3160 (6.2)	43
Palestine	32	155	1 (0.6)	0.2
Morocco	31	676	39 (5.8)	2
Jordan	31	278	5 (1.8)	0.5
Israel	31	6211	31 (0.5)	6
Pakistan	30	2291	31 (1.3)	0.2
Algeria	28	847	58 (6.8)	3
Egypt	26	779	52 (6.8)	0.8
Saudi Arabia	26	1720	16 (0.9)	1.0
Bahrain	26	635	4 (0.6)	2
+/- 25 Degrees Latitude				
Qatar	25	835	2 (0.2)	1
Taiwan	24	339	5 (1.5)	0.2
Cuba	23	212	6 (2.8)	0.7
India	22	2032	58 (2.8)	0.07
Mexico	22	1378	37 (2.7)	0.6
Hong Kong	22	802	4 (0.5)	0.5
Oman	21	231	1 (0.4)	0.4
Dominican Republic	18	1284	57 (4.4)	8
Guadeloupe	16	125	6 (4.8)	17
Honduras	15	219	14 (6.4)	2
Martinique	15	135	3 (2.2)	11
Thailand	15	1875	15 (0.8)	0.3
Senegal	14	195	1 (0.5)	0.1
Philippines	13	2633	107 (4.1)	1
Burkina Faso	12	282	16 (5.7)	0.8
Brazil	10	6931	244 (3.5)	2

(Continues)

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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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

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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