

COVIDAge Risk Calculator – Rationale for a Vitamin D Biometric

Peter F. Lenehan, MD PhD, Chief Medical Officer – 14 Sep 2020

Everist Health's COVIDAge Risk Calculator (CARC) is designed to assess an individual's risk for adverse outcomes from a COVID-19 infection should one become infected with the SARS-CoV-2 virus and to provide the user with suggestions on how to lower that risk, based on best available evidence. It currently does NOT assess an individual's risk for becoming infected with SARS-CoV-2. The risks for COVID-19 related hospitalization, ICU admission, and mortality are determined based on the cumulative contributions of multiple CARC biometrics, one of which is **serum Vitamin D [25(OH)D] level**.

Vitamin D (Vit D) is a fat-soluble vitamin that plays a key role in calcium metabolism, neuromuscular and immune function, and reduction of inflammation. **Serum Vit D [25(OH)D] insufficiency** (20 to <30 ng/ml; 50 to <75 nmol/L) and **deficiency** (<20 ng/ml; <50 nmol/L) have been strongly linked to poor outcomes from COVID-19 infection, thought to be mainly consequent to associated endothelial dysfunction and the lack of an optimal immune response to the SARS-CoV-2 virus [1,2,3].

Among the most notable documented correlations between Vit D insufficiency/deficiency and COVID-19 outcomes are:

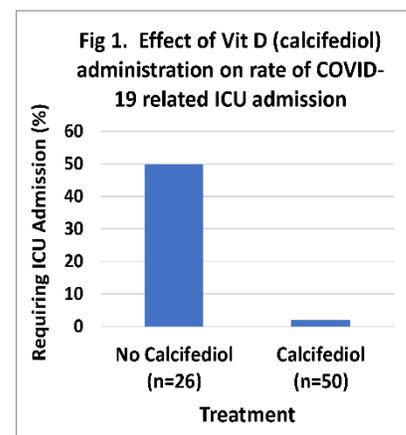
- 1) a correlation between COVID-19 severity and geographic latitude that overlaps the pattern of seasonal Vit D deficiency [4];
- 2) a higher mortality risk for COVID-19 patients with acute respiratory failure who have severe Vit D deficiency [5];
- 3) a role for Vit D in suppressing cytokine storm and associated mortality in COVID-19 patients [6].

Because the COVID-19 pandemic has existed since only the beginning of 2020, the world's COVID-19 literature is, consequently, predominated by publications from small-scale investigations that report observations and retrospective analyses involving a wide variety of patient populations, both with COVID-19 and/or at risk of contracting it. Although many prospective investigations of the relationship between Vit D and COVID-19 are already, or soon-to-be, underway (48 such studies are currently registered in <https://ClinicalTrials.gov>, half of which are studying the therapeutic benefit of administered Vit D in COVID-19), results from many of these larger studies, unfortunately, may become available only well after the COVID-19 pandemic has become much less of a public health threat – thereby lessening their impact on COVID-19 patient care.

Fortunately, peer-reviewed reports are already beginning to emerge of **randomized, prospective** Vit D therapeutic studies in COVID-19, along with **meta-analyses** of recently published investigations of the effect of Vit D on COVID-19 outcomes. Representative of these are:

➤ Castillo *et al* (Aug 2020) [7]:

- Prospective, parallel randomized control clinical trial comparing best available therapy + high dose oral calcifediol [25(OH)Vit D] vs best available therapy alone in consecutive patients hospitalized with COVID-19 infection (n=76; 59% M; mean age: 53 ± 10 yrs).
- *Results (Fig 1)*: Multivariate risk estimate odds ratio for ICU admission in patients with calcifediol treatment vs no calcifediol treatment = 0.03 (95% CI: 0.003 to 0.25, p<0.001), i.e., an estimated 97% reduction in the risk of ICU admission (2% vs 50%)
- *Conclusion*: Giving high dose 25(OH)Vit D to hospitalized COVID-19 patients significantly reduced their need for ICU admission and appeared to reduce the severity of their infection.



➤ Munshi *et al* (Jul 2020) [8]:

- Meta-analysis of 8 datasets from 7 international COVID-19 clinical studies assessing the relationship of serum Vit D levels with COVID-19 outcomes (n=1,368; 57% M; pooled mean age: 64 ± 7 yrs).
- *Results (Fig 2)*: Patients with poor prognoses (n=634; severe symptomology, ICU admission, or death) had significantly lower serum levels of Vit D compared to those with good prognoses (n=669), representing an adjusted standardized mean difference of **-5.12 nmol/L** (95% CI: -9.14 to -1.10, p=0.012); mean serum Vit D level = 22.9 nmol/L (9.2 ng/mL). Pairwise comparison of patient cohorts with poor vs good prognoses showed no significant differences for age, gender, hypertension, diabetes, congestive heart failure, or COPD.
- *Conclusion*: Serum Vit D level appears to afford independent information concerning a patient's potential for developing severe COVID-19 infection.

Study (all 2020)		Country	Poor Outcome			Good Outcome		
			N	Mean [Vit D] (nmol/L)	1 SD	N	Mean [Vit D] (nmol/L)	1 SD
Alipio et al	Apr 9	Philippines	104	19.3	0.6	108	29.1	0.5
Raharusuna et al	Apr 26	Indonesia	380	18.2	0.6	400	32.2	1.2
Lau et al	Apr 28	USA	13	19.2	10.8	7	29.8	13.3
Avolio et al	May 9	Switzerland	27	13.4	9.5	80	21.3	16
Tian et al	May 13	China	13	19.2	10.8	7	29.8	13.3
Faul et al	May 15	Ireland	12	27	12	21	41	19
De Smet	May 19	Belgium	85	17.8	8.3	46	22.2	10.8

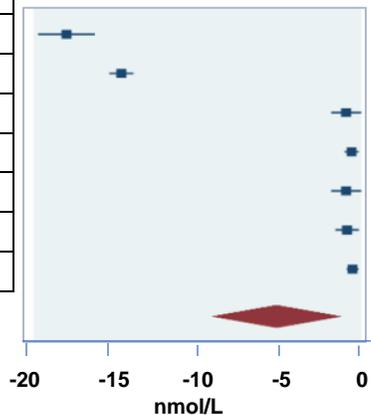


Figure 2. Pooled estimate comparing COVID-19 patients with poor vs good prognosis

SUMMARY

The Vit D biometric in the CARC serves the purpose of providing the user with information about a modifiable health condition that, based on best available scientific and clinical evidence, can be used to help estimate one's risk for adverse outcomes should that individual become infected with SARS-CoV-2. This is based on strong indirect and, now, emerging direct evidence from multiple international studies, including those highlighted here.

To exclude this biometric from the CARC while awaiting more definitive large-scale studies would deprive the user of receiving information upon which they could quickly act now, at their discretion, while the threat of adverse outcomes to a COVID-19 infection remains most relevant. The potential benefit of avoiding Vit D deficiency clearly outweighs the minimal potential risk of excessive Vit D dosing.

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