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Serum Levels of Vitamin C and Vitamin D in a Cohort of Critically Ill COVID-19 Patients of a North American Community Hospital Intensive Care Unit in May 2020: A Pilot Study ☆

Cristian Arvinte, MD [a,*], Maharaj Singh, PhD [b,c], Paul E. Marik, MD, FCCP, FCCM [d]

[a] Intensivist & Pulmonologist, North Suburban Medical Center, Thornton, Colorado 80229, USA
[b] Research Assistant Professor, Biostatistics, Research and Graduate Studies, Marquette University, School of Dentistry, Milwaukee, Wisconsin 53201, USA
[c] Biostatistician Senior, Advocate Aurora Research Institute, Advocate Aurora Health Care, Milwaukee, Wisconsin, 53233, USA
[d] Chief, Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, Norfolk, Virginia 23507, USA

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ABSTRACT

Background: The COVID-19 pandemic has placed an enormous and growing burden on the population and health infrastructure, warranting innovative ways to mitigate risk of contracting and developing severe forms of this disease. A growing body of literature raises the issue of vitamin C and vitamin D as a risk-assessment tool, and therapeutic option, in COVID-19.

Objective: The objective of this pilot study was to measure serum vitamin C and vitamin D levels in a cohort of patients with critical COVID-19 illness in our community hospital ICU, correlate with other illness risk factors (age, BMI, HgbA1c, smoking status), generate hypotheses, and suggest further therapeutic intervention studies.

Method: This pilot study included all 21 critically ill COVID-19 patients hospitalized in May 2020 in the ICU of North Suburban Medical Center, Thornton, Colorado, in whose care the principal investigator (C.A.) was involved. We measured patients' serum vitamin C and vitamin D levels, and standard risk factors like age, BMI, HbA1c, and smoking status. Variables in this study were gauged using descriptive statistics.

Results: Of 21 critically ill COVID-19 patients (15 males and 6 females, 17 Hispanic and 4 Caucasian, of median age 61 years, range 20–94), there were 11 survivors.

Serum levels of vitamin C and vitamin D were low in most of our critically ill COVID-19 ICU patients.

Older age and low vitamin C level appeared co-dependent risk factors for mortality from COVID-19 in our sample. Insulin resistance and obesity were prevalent in our small cohort, but smoking was not.

Conclusion: Our pilot study found low serum levels of vitamin C and vitamin D in most of our critically ill COVID-19 ICU patients. Older age and low vitamin C level appeared co-dependent risk factors for mortality. Many were also insulin-resistant or diabetic, overweight or obese, known as independent risk factors for low vitamin C and vitamin D levels, and for COVID-19.

These findings suggest the need to further explore whether caring for COVID-19 patients ought to routinely include measuring and correcting serum vitamin C and vitamin D levels, and whether treating critically ill COVID-19 warrants acute parenteral vitamin C and vitamin D replacement.

1. Introduction

The SARS-CoV-2 coronavirus disease was reported in 2019 (COVID-19), reached pandemic extent in 2020, and has placed an enormous and growing burden on the population at large, and on the health infrastructure. The challenge posed by the multisystemic morbidity of COVID-19, and its high infectivity, calls for research on innovative ways to detect and mitigate the risk factors leading to contracting and developing severe forms of COVID-19.

Whereas the role of nutrition in health and illness had been intuited since ancient times; description of rickets dates back to the 17th century; official nutritional mandates to prevent scurvy were first issued in the 18th century and were conceptualized in medical science over 100 years ago [1]; the discoveries of vitamin C and vitamin D and their physiologic roles in the 1920s were landmarks in recognizing nutrition's formal legitimacy in modern conventional medicine.

Despite established guidelines on Reference Daily Intake (RDI) for both vitamin C and vitamin D and availability of fortified foods, chronic deficits

* Corresponding author.
E-mail addresses: carvinte@msn.com, (C. Arvinte), maharaj.singh@marquette.edu, (M. Singh), marikpe@evms.edu. (P.E. Marik).

were documented in the general population [2,3], and in the in-hospital patients [4]. The biological culprit behind the risk of vitamin C deficit is the human species' maladaptive evolutionary mutation of losing its ability to synthesize vitamin C endogenously [5].

There is evidence associating low body reserves of vitamin C and vitamin D with relative immune deficit and higher risk of infections [6,7].

Consequently, there is growing support for interventions aimed at raising body reserves of vitamin C, with clinical benefits shown in viral illnesses [8], sepsis [9], and critical illness [10].

Interventions aimed at raising reserves of vitamin D, while suggestive of a role in preventing viral infections [1–3,11], are awaiting confirmation of a role for acute oral/enteral supplementation in acute critical illness [12].

The current COVID-19 pandemic provides an opportunity to explore whether deficits in vitamin C and/or vitamin D increase the risk of SARS-CoV-2 infection, or poor outcomes in COVID-19, and whether acute supplementation of vitamin C and/or vitamin D modifies those risks [13,14].

This pilot study aimed to measure serum vitamin C and vitamin D levels in a cohort of patients with critical COVID-19 illness in our community hospital ICU, correlate with other illness risk factors (age, BMI, HgbA1c, smoking status), generate hypotheses, and suggest further therapeutic intervention studies.

2. Method

This pilot study included all 21 critically ill COVID-19 patients hospitalized in May 2020 in the ICU of North Suburban Medical Center, Thornton, Colorado, in whose care the principal investigator (C.A.) was involved. Their demographics are shown in the Tables below. All patients had consented to standard of care investigation and treatment. Collection of lab samples, including serum vitamin C and vitamin D levels, were part of the routine immunologic assessment of their severe infectious disease. All variables in this study were described using descriptive statistics. To compare serum level for survivors and non-survivors we used *t*-test for independent samples. For all statistical tests, an alpha level of 0.05 or less was considered statistically significant. All statistical analysis was done using SAS 9.4 version, SAS Institute, Cary, NC.

3. Results

Of our 21 critically ill COVID-19 patients, 11 survived (48% mortality).

Patients' demographic data and vitamin C and D levels are provided in Table 1 and Fig. 1.

Serum levels of vitamin C and vitamin D2 and D3 were low in most patients of our cohort, compared with the normal ranges in our hospital laboratory for vitamin C (17–154 μmol/L) and vitamin D2 and D3 (30–100 ng/mL).

Age appeared to be a predictor of mortality from COVID-19. Every 10-years' increase in age increased risk of death 2.7-fold (OR = 2.7, 95% CI = 1.01–5.10 p = 0.0474).

Older age and low vitamin C level appeared co-dependent risk factors for mortality from COVID-19 in our sample, as suggested by Figs. 2 and 3.

We used age and serum vitamin C level as predictors of mortality in three separate regression models.

-Firstly, age was used as a predictor of mortality in univariate regression model, and the results showed that increasing age significantly predicted mortality.

-Secondly, we used serum vitamin level C as predictor of mortality in univariate regression model, and results showed that serum vitamin C was not a significant predictor of mortality (Fig. 2).

-In the third multivariate regression model, we included both age and serum level vitamin C in the model, and the results showed that both age and serum level were non-significant predictors of mortality (Fig. 3).

Overall correlation coefficient between age and vitamin C level was -0.2531 (p = 0.2816)

Survivors' correlation coefficient between age and vitamin C level was -0.1954 (p = 0.5885)

Non-survivors' correlation coefficient between age and vitamin C level was 0.1676 (p = 0.6435)

None of the above correlation coefficients were statistically significant.

Age was an independent predictor of mortality only when serum vitamin C level was not included in the regression model. When serum vitamin C level was added as a predictor, along with age, both variables became non-significant predictors of mortality. This suggests an indirect evidence that some of the significant contribution of age to mortality came from the serum vitamin C level (Fig. 3). Thus, age became non-significant after introduction of serum level in the regression model.

In other words, age without filtering out the effect (unadjusted) of serum vitamin C level (both age and vitamin C were contributing to mortality) was a significant predictor of mortality. However, when effect of serum vitamin C was taken out (adjusted), age became non-significant predictor mortality. This suggests that, in fact, serum vitamin C level contributed to the significance of age being predictor of mortality.

Insulin resistance and obesity were prevalent in our small cohort, with a mean HbA1c of 7.6, and a mean BMI of 32.

Active smoking was surprisingly and encouragingly rare in our cohort, with only 1 out of 21 patients smoking at the time of admission.

4. Discussion

In this small pilot research study, most of our critically ill COVID-19 patients had low serum levels of vitamin C and vitamin D. The normal ranges used by our hospital laboratory for vitamin C (17–154 umol/L) and vitamin D2 and D3 (30–100 ng/mL) are overly broad, which might underestimate

Table 1

Description of cohort of critically ill COVID patients admitted to this community ICU.

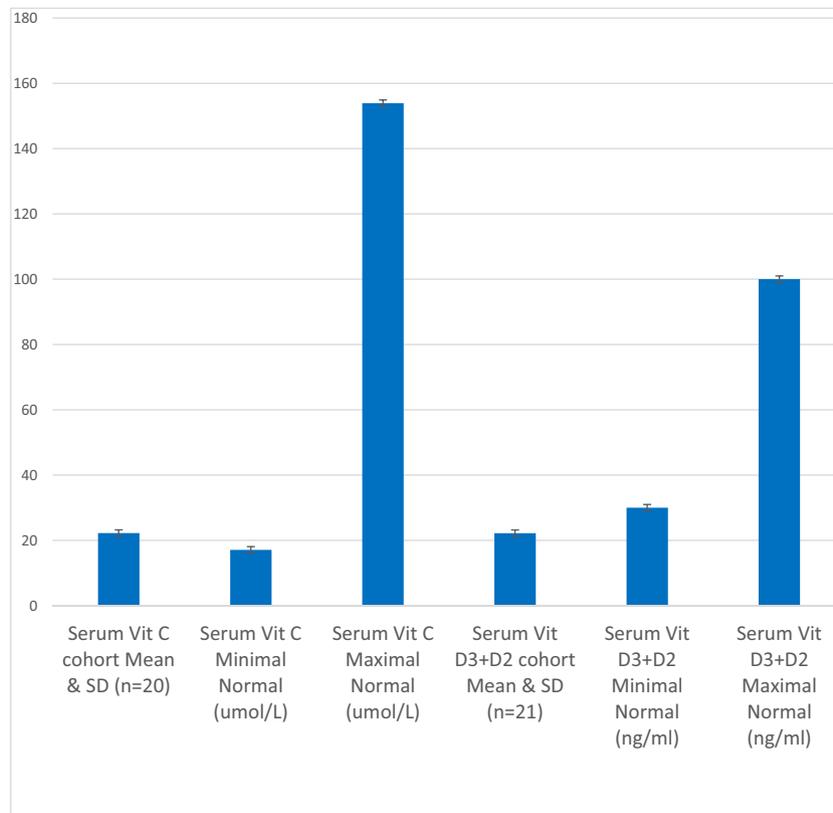| Patient characteristic	Total (N = 21)	Survivor (N = 11)	Non-survivor (N = 10)	p-Value
Gender (N, %)				0.8901
Female	6 (28.6%)	3 (27.3%)	3 (30.0%)	
Male	15 (71.4%)	8 (72.7%)	7 (70.0%)	
Race (N, %)				0.0902☐
Caucasian	4 (19.1%)	4 (36.4%)	0 (0.0%)	
Hispanic	17 (80.9)	7 (63.6%)	10 (100.0%)	
Age years (mean, SD)	60.2 (17.4)	52.2 (15.3)	69.1 (15.5)	**0.0215**
BMI (mean, SD)	31.6 (7.3)	32.7 (7.1)	30.2 (7.6)	0.4593
HgbA1c (mean, SD)	7.6 (2.0)	8.0 (2.5)	7.2 (1.2)	0.4059
Vitamin C level μmol/L (mean, SD)	22.2 (18.3)	29.1 (23.3)	15.4 (7.6)	0.1063
Vitamin D_2 D_3 ng/mL (mean, SD)	22.0 (9.5)	21.3 (11.3)	22.8 (7.7)	0.7242

☐ p Value for Fisher exact test.

Fig. 1. Serum levels of vit C (μmol/L) and vit D (ng/mL) in critically ill COVID-19 ICU patients, and reference lab ranges.

the vitamin C and vitamin D deficits of the general population, and our study sample.

Many patients in our cohort were insulin-resistant or diabetic, which is a risk factor for low vitamin C and vitamin D levels, and for COVID-19 [3,6,11].

Many patients in our cohort were overweight or obese, which is also a risk factor for low vitamin C and vitamin D levels, and for COVID-19 [2,3,7].

Most of our critically ill COVID-19 patients were non-white (17 Hispanic, 4 white), disproportionate to the local demographics of our hospital's suburban Colorado community, suggesting a higher risk of COVID-19 morbidity for Hispanics. Populational studies report a higher incidence of

vitamin D deficit in individuals with darker skin tones [7], and our study results may correlate with that observation. Of note, African Americans are only a small demographic fraction in our hospital's suburban Colorado community, and none was present in this cohort.

Older age and low vitamin C level appeared co-dependent risk factors for mortality from COVID-19 in our sample, which is in line with the international experience [6]. Irrespective of all unknown covariates, serum vitamin C contributed to the significance of age as a predictor of mortality (conversely, without a serum vitamin C level, age became non-significant).

Our study has several limitations. The study sample was too small to detect statistically significant differences in serum vitamin C and vitamin D levels between survivors and nonsurvivors.
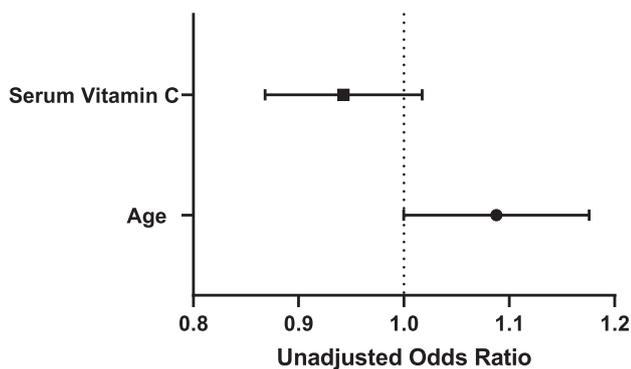

Fig. 2. Univariate (unadjusted) odds ratios for mortality as outcome, and age, and level of serum vitamin C as separate (one at a time) predictors among patients diagnosed with COVID-19, using two separate regression models. When age, and all other unknown covariates, and serum vitamin C level are considered, age becomes a significant predictor of mortality.
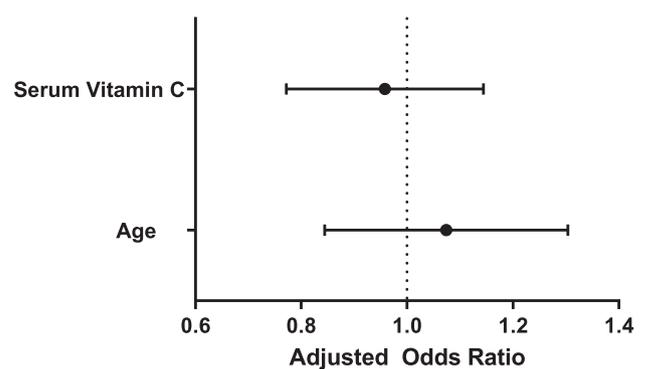

Fig. 3. Multivariate (adjusted) Odds ratios for mortality as outcome, and age, and level of serum vitamin C (together), as predictors among patients diagnosed with COVID-19, using multivariate regression model. When age and all other unknown covariates are considered, but serum vitamin C level is not, age becomes a non-significant predictor of mortality.

Our study lacked a *longitudinal, pre-morbid* follow-up of serum vitamin C and vitamin D levels in the same cohort, or a control group of serum vitamin C and vitamin D levels in *healthy* subjects *matched* for demographics and other risk factors, which precludes firm conclusions whether low serum levels of vitamin C and vitamin D are a *risk factor for*, versus a *consequence of,* acquiring SARS-CoV-2, or having a severe form of COVID-19. Critical illness is often associated with low serum vitamin C levels, due to metabolic consumption. However, we cannot exclude the possibility that chronic, pre-existing low serum vitamin C levels may increase the risk for, and severity of, COVID-19 [18].

The findings of our small pilot study might generate hypotheses, and contribute impetus for further therapeutic intervention studies, with questions like:

- Should those at risk for, or newly diagnosed with, SARS-CoV-2 infection have their serum vitamin C and vitamin D levels measured, and started on pre-emptive supplementation to lower risk of COVID-19, and severe forms [3,11]?
- Should those infected with SARS-CoV-2, and with additional risk factors (the elderly, diabetics, and/or obese) receive rapid and higher-dose replacement and supplementation of vitamin C and vitamin D, to lower risk of COVID-19, and severe forms [5,9,11,12]?
- Should those with severe or critical COVID-19, and whose critical illness might *impair the enteral absorption* of vitamin C [10] and vitamin D [16], receive *urgent, parenteral, high-dose* replacement and supplementation of vitamin C [4,9,10,13,15] and vitamin D [14,16,17]?

5. Conclusion

This pilot study found low serum levels of vitamin C and vitamin D in most of our critically ill COVID-19 ICU patients. Older age and low vitamin C level appeared co-dependent risk factors for mortality.

Many were also insulin-resistant or diabetic, overweight or obese, which had been reported as independent risk factors for low vitamin C and vitamin D levels, and for COVID-19.

These findings suggest the need to further explore whether caring for COVID-19 patients ought to routinely include measuring and correcting serum vitamin C and vitamin D levels, and whether treating critically ill COVID-19 warrants acute parenteral vitamin C and vitamin D replacement.

Ethical Approval and Informed Consent

The work involved in conducting our research has followed standard medical ethical rules and regulations.

Authors' Individual Contributions by "CRediT" Criteria:

Cristian Arvinte: Investigation, Methodology, Writing (original draft preparation);

Maharaj Singh: Data Curation, Formal Analysis, Validation, Methodology, Software;

Paul E. Marik: Conceptualization, Supervision, Reviewing, Editing;

Declaration of Competing Interest

The authors of this paper have had no conflicts of interest in conducting and publishing this research.

References

[1] Incipient Scurvy. Lancet. 22 September 1917;190(Issue 4908):465–6. https://doi.org/10.1016/S0140-6736(01)52008-5.

[2] Schleicher RL. Serum vitamin C and the prevalence of vitamin C deficiency in the United States: 2003–2004 National Health and Nutrition Examination Survey (NHANES). Am J Clin Nutr. 2009;90:1252–63. https://doi.org/10.3945/ajcn.2008.27016.

[3] McCartney DM, Byrne DG. Optimization of Vitamin D Status for Enhanced Immuno-protection Against Covid-19. Ir Med J. 2020;113(4):58http://www.indymedia.ie/attachments/may2020/covid-19_vit_d_irish_med_j_mccartney.pdf.

[4] Carr AC, Rosengrave PC, Bayer S, et al. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit Care. 2017;21:300. https://doi.org/10.1186/s13054-017-1891-y.

[5] Marik PE. Vitamin C: an essential "stress hormone" during sepsis. J Thorac Dis. February 2020;12(Supplement 1) (Sepsis: Science and Fiction) http://jtd.amegroups.com/article/view/34870/html.

[6] Carr AC, Maggini S. Vitamin C and immune function. Nutrients. 2017;9(11):1211https://www.mdpi.com/2072-6643/9/11/1211/htm.

[7] Kohlmeier Martin. Avoidance of vitamin D deficiency to slow the COVID-19 pandemic. BMJ Nutrition, Prevention & Health. 2020;0. https://doi.org/10.1136/bmjnph-2020-000096.

[8] Biancatelli R, Berrill M, Marik P. The antiviral properties of vitamin C. Expert Rev Anti-Infect Ther. 2020;18(2):99–101. https://doi.org/10.1080/14787210.2020.1706483.

[9] Marik Paul E. Vitamin C for the treatment of sepsis: The scientific rationale. Pharmacol Ther. 2018;189:63–70. https://doi.org/10.1016/j.pharmthera.2018.04.007.

[10] Long M, et al. Dosing matters! Vitamin C in critical illness. Crit Care Med. December 2019;47(Issue 12):e1042https://journals.lww.com/ccmjournal/Citation/2019/12000/Dosing_Matters__Vitamin_C_in_Critical_Illness.53.aspx.

[11] Grant W, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 2020;12:988https://www.mdpi.com/2072-6643/12/4/988/htm.

[12] The National Heart. Lung, and Blood Institute PETAL Clinical Trials Network: early high-dose vitamin D3 for critically ill, vitamin D–deficient patients. N Engl J Med. 2019;381:2529–40https://www.nejm.org/doi/full/10.1056/NEJMoa1911124.

[13] Renyi Wu, et al. l: An update on current therapeutic drugs treating COVID-19. Cur Pharmacol Rep. 11 May 2020;12(4):1–19 988 https://www.mdpi.com/2072-6643/12/4.

[14] Silberstein Morrie. Vitamin D: A simpler alternative to tocilizumab for trial in COVID-19? Med Hypotheses. 2020;140:109767https://www.sciencedirect.com/science/article/pii/S0306987720305454.

[15] Oudemans-van Straaten HM, Man AMS, de Waard MC. Vitamin C revisited. Crit Care. 2014;18:460. https://doi.org/10.1186/s13054-014-0460-x.

[16] Dwivedi A, et al. Parenteral vitamin D supplementation is superior to oral in vitamin D insufficient patients with type 2 diabetes mellitus. Diabetes Metab Syndr Clin Res Rev. November 2017;Volume 11(Supplement 1):S373–5. https://doi.org/10.1016/j.dsx.2017.03.019.

[17] Einarsdóttir K, et al. Effect of a single 'megadose' intramuscular vitamin D (600,000 IU) injection on vitamin D concentrations and bone mineral density following biliopancreatic diversion surgery. Obes Surg. 2010 Jun;20(6):732–7. https://doi.org/10.1007/s11695-009-0024-3.

[18] Chiscano-Camón L, et al. Vitamin C levels in patients with SARS-CoV-2–associated acute respiratory distress Syndrome. Crit Care. 2020;24:522. https://doi.org/10.1186/s13054-020-03249-y.