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Short Communication

COVID-19 mortality is associated with low vitamin D levels in patients with risk factors and/or advanced age

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SUMMARY

Background & aims: Although conclusive evidence is yet lacking, it has been suggested that vitamin D deficiency (VD) may be associated with a more severe course of SARS-CoV-2 Infection (COVID-19). In this retrospective study we assessed the association of VD deficiency with mortality in a group of COVID-19 patients treated in a tertiary referral center.
Methods: Data of 257 Covid-19 patients hospitalized between 30th September 2020 and 2nd March 2021 have been collected retrospectively. The following parameters were collected: age, gender, serum level of 25-OH-Vitamin D_3, outcome (survival/death), comorbidities (cancer, diabetes mellitus and chronic obstructive pulmonary disease). Serum VD measurement was done within 3 days of admission.
Results: VD levels were significantly lower in patients who did not survive, however, in this patients' group the average age was significantly higher than among those, who survived. After age-matching, in a subgroup of patients with risk factors and/or 60 years of age or older who survived had significantly higher VD level in their serum than those who deceased. Serum C-reactive protein, lactate-dehydrogenase and creatinin-kinase were significantly higher in the group in which the patients died, however these laboratory parameters did not correlate with the VD levels.
Conclusion: We found that in COVID-19 infection, when old age as risk factor (60 years of age or older) was pooled with risk factors (cancer, diabetes and/or COPD), the VD levels were significantly lower in the patient group, in which the patients did not survive. We suggest further, prospective studies in similar subgroups to explore a possible causal relationship.
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1. Introduction

Since vitamin D (VD) supplementation of 400–1000IU/day seems to have a modest protective effect for acute respiratory infections [1], it has been suggested that VD deficiency may be associated with a more severe course of SARS-CoV-2 infection (COVID-19) [2]. In a recent review [3] the authors concluded that high-quality evidence is currently lacking, but there is suggestive evidence for an immunomodulatory role of vitamin D for

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respiratory infections and contextual evidence of the shared risk factors between vitamin D deficiency and COVID-19 infection outcome: older age, obesity, and minority ethnicity. It has been shown that airway diseases are associated with dysregulated vitamin D metabolism, raising the possibility that vitamin D deficiency might arise because of pulmonary inflammation [4] and the results of studies on low pre-pandemic 25(OH)D levels and subsequent incidence and severity of COVID-19 were conflicting [5,6]. In this retrospective study we assessed the association of VD deficiency with mortality in a group of COVID-19 patients treated in a tertiary referral center.

2. Materials, methods

Anonymized data of 257 Covid-19 patients (131 men; 126 women, average age 67 (min:22 - max:97)) hospitalized between 30th September 2020 and 2nd March 2021 at the Department of Pulmonology, Petz Aladár University Teaching Hospital, Győr, Hungary have been collected retrospectively. The study was approved by the institutional review board of the Petz Aladár University Teaching Hospital, Győr, Hungary (PAMOK Hospital Protocol No: 76-1-12/2021; 76-1-13/2021). The study protocol was in accordance with the ethical standards established in the 1964/2013 (7th revision) Declaration of Helsinki for research involving human subjects. The following parameters were collected: age, gender, serum level of 25-OH-Vitamin D_3, outcome (survival/death), comorbidities (cancer, diabetes mellitus and chronic obstructive pulmonary disease). 45 patients did not need oxygen supplementation, 221 patients received oxygen, 32 patients were admitted to the intensive care unit and received invasive ventilation. The patients received daily 2000 IU Vitamin D3 (cholecalciferol). Serum VD measurement was done within 3 days of admission (on the first weekday) and VD was administered on the day of admission. Serum VD measurement was done using the ADVIA Centaur System, equimolar measurement of total 25(OH), Vitamin D_2 and D_3. Power analysis of required sample size revealed that a minimum 56 subjects/group would be required to reach a significance level of $p < 0.05$.

3. Results

In Fig. 1. We show the VD levels according to age in all patients, with or without risk factors and in Table 1 we list the main statistical results.

We carried out several subgroup analyses in order to examine eventual differences in VD levels according to age under or over 60 years and risk factors. VD levels were significantly lower in patients who did not survive and were 60 years of age or older, however, in this patients' group the average age was significantly higher than among those, who survived. In the younger patients' groups (under 60 years of age) there was no significant difference in VD levels between the groups created according to survival.

As a next analysis, matched groups were built ('recovered versus deceased') considering old age in itself as risk factor by including patients with risk factors and/or patients who were 60 years or older (with or without risk factors). Age-matching was done by randomly including a patient with the same age into the group of recovered patient for every patient in the deceased group. Then the VD serum level was compared between groups. The results are shown in Table 2. The patients with risk factors and/or 60 years of age or older who survived had significantly higher VD level in their serum than those who deceased.

4. Discussion

Our results show that summary mortality statistics including all hospitalized patients tend to obscure differences of pre-infection VD status between subgroups 'survived/died', because VD levels tend to be lower in elderly patients or in patients with other risk factors, who also are dying of the infection more frequently. A subgroup analysis showed that among patients younger than 60 years of age with or without risk factors there was no difference in VD level between

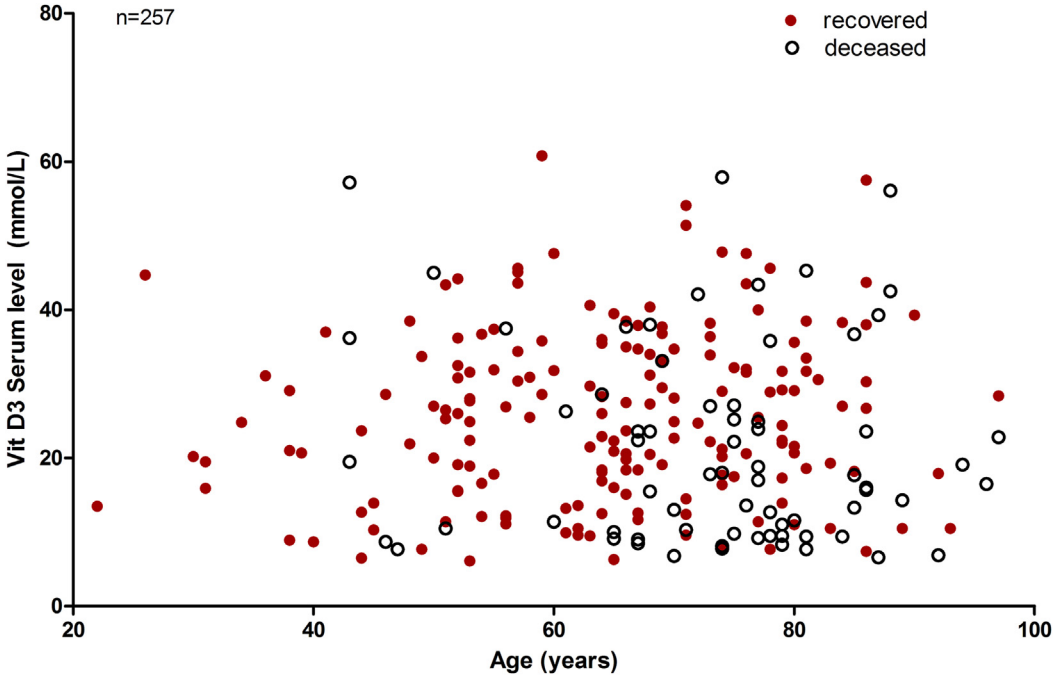

Fig. 1. Legend: Left panel: VD-level dependence of mortality (empty circles: deceased, dots: recovered).

Table 1
Mortality rates and VD levels.

Mortality rate	27.6%
VD-level all patients (mean ± SD)	25 ± 12 (n = 257)
VD-level recovered (mmol/L) (mean ± SD)	26 ± 12[a](n = 186)
VD-level deceased (mmol/L) (mean ± SD)	21 ± 13 (n = 71)
Age recovered (mean age in years ± SD)	65 ± 14[a]
Age deceased (mean age in years ± SD)	74 ± 13
Subgroups	
VD-level in patients who recovered and were 60 years of age or older (mean age: ± SD: 73 ± 13[a])	26 ± 11[a] (n = 120)
VD-level in patients who deceased and were 60 years of age or older (mean age: 77 ± 11)	20 ± 13 (n = 63)
VD-level, patients recovered, younger than 60 years (mean ± SD)	26 ± 6 (n = 66) ns
VD-level, patients deceased, younger than 60 years (mean ± SD)	27 ± 8 (n = 8)

ns = no significant difference between this value and the value below.
[a] Significant difference between this value and the value below (unpaired t-test, $p < 0.001$).

Table 2
Mortality rates and VD levels in age-matched groups with risk factors and/or 60 years of age or older.

	Patients with risk factors and/or 60 years of age or older
VD-level recovered (mmol/L) (mean ± SD)	30 ± 12[a](n = 65)
VD-level deceased (mmol/L) (mean ± SD)	21 ± 13 (n = 65)
Age recovered all cases (mean age in years ± SD)	76 ± 9
Age deceased all cases (mean age in years ± SD)	77 ± 10

[a] Significant difference between VD-level of recovered patients and deceased patients with risk factors (unpaired t-test, $p < 0.001$; $d = 0.737$, statistical power: 98.4%).

surviving or deceased patients. However, when old age (60 years of age or older) was pooled with risk factors (cancer, diabetes and/or COPD), the VD levels were significantly lower in the patient group, in which the patients did not survive. Although there is an abundance of papers on the potential connection between VD-deficiency and poor survival in COVID-19 in literature, the existence of such a connection has not been proven conclusively. According to several more recent publications in which higher case numbers have been examined, VD insufficiency or deficiency was also not independently associated with either COVID-19 infection or linked to mortality. Hastie et al. [6] examined more than 300 000 patients from the UK Biobank, 449 of which had confirmed COVID-19 infection. Their data did not support a potential link between vitamin D concentrations and risk of COVID-19 infection. Patchen et al. applied a two-sample Mendelian randomisation in 17 965 COVID-19 cases and over one million control cases and concluded that genetically predicted differences in long-term vitamin D nutritional status did not causally affect susceptibility to and severity of COVID-19 infection [7]. Szeto et al. evaluated VD level in 93 patients and did not find relationship between prehospitalization vitamin D status and COVID-19 clinical outcomes [8]. We suggest further investigations in specific subgroups consisting of elderly patients and/or risk factors to explore the role of VD-deficiency in COVID-19 and other respiratory infections. VD levels are lower when there is an inflammation in the body [9], therefore we supply data as supplemental material summarizing inflammatory laboratory parameters in the two groups. Serum C-reactive protein, lactate-dehydrogenase and creatinin-kinase were significantly higher in the group in which the patients died; D-dimer, troponin, ferritin, procalcitonin and lymphocyte counts were not different between the two groups. We carried out a correlation analysis between serum VD-level and CRP, CK and LDH, however these laboratory parameters did not correlate with the VD levels (suppl. material, Table 4). This means in our view that a simple relationship between inflammation and low VD levels could not be found. Based on our dataset, it cannot be decided if patients who did not survive had low VD-levels because of their advanced age and/or risk factors and they had a worse outcome independently of the VD status, or perhaps there exists a causal relationship. This issue may be examined by prospective studies in which VD substitution is given.

5. Conclusion

We found that in COVID-19 infection, when old age (60 years of age or older) was pooled with risk factors (cancer, diabetes and/or COPD), the VD levels were significantly lower in the patient group, in which the patients did not survive. We suggest further, prospective studies in similar subgroups to explore a possible causal relationship.

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Author contributions

TT,SJ,LTT,ÁP,MK,IH,ID,ZSZS,TFM,BB: conceptualization; TT,SJ, LTT,ÁP,MK,IH,ID,ZSZS: data collection; SJ,BB: formal analysis; TT,SJ,LTT,ÁP,MK,IH,ID,ZSZ,: methodology; JT: Project administration; TT,SJ,LTT,ÁP,MK,IH,ID,ZSZS,TFM,BB: Writing - original draft.

Declaration of competing interest

The authors do not declare any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2021.11.025.

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