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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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S U M M A R Y

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 D₃, outcome (survival/death), comorbidities (cancer, diabetes mellitus and chronic obstructive pulmonary disease). Serum VD measurement was done within 3 days of admission. We found that in COVID-19 infection, when old age as risk factor (60 years of age or older) and/or chronic obstructive pulmonary disease), the VD levels were significantly higher in those patients who did not survive. 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
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 D₃, 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 D₂ and D₃. 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...
associated with either COVID-19 infection or linked to mortality. examined, VD insuf ciently in several recent publications in which higher case numbers have been connection has not been proven conclusively. According to several poor survival in COVID-19 in literature, the existence of such a COPD), the VD levels were signi cantly 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-deiciency 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 insuf ciency or de ciency was also not independently associated with either COVID-19 infection or linked to mortality. Hazie et al. [6] examined more than 300 000 patients from the UK Biobank, 449 of which had conirmed 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 nd relationship between prehospitalization vitamin D status and COVID-19 clinical outcomes [8]. We suggest further investigations in speci c subgroups consisting of elderly patients and/or risk factors to explore the role of VD-deiciency in COVID-19 and other respiratory infections. VD levels are lower when there is an inammation in the body [9], therefore we supply data as supplemental material summarizing inammatory laboratory parameters in the two groups. Serum C-reactive protein, lactate-dehydrogenase and creatininkinase were signi cantly 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 inammation 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 signi cantly 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, LT, ÅP, MK, IH, ID, ZSZ, TFMB: conceptualization; TT, SJ, LT, ÅP, MK, IH, ID, ZSZ: data collection; SJ, BB: formal analysis; TT, SJ, LT, ÅP, MK, IH, ID, ZSZ: methodology; JT: Project administration; TT, SJ, LT, ÅP, MK, IH, ID, ZSZ, TFMB: Writing - original draft.

Declaration of competing interest

The authors do not declare any conicts 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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