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ORIGINAL CONTRIBUTION

# Association between vitamin D deficiency and post-acute outcomes of SARS-CoV-2 infection

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## Abstract

**Objectives** This study aimed to investigate the association between vitamin D deficiency (VDD) and post-acute outcomes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

**Methods** This retrospective study used the TriNetX research network to identify COVID-19 patients between January 1 and November 30, 2022. Patients were matched using propensity score matching (PSM) and divided into VDD (< 20 ng/mL) and control (≥ 20 ng/mL) groups. The primary outcome was a composite of post-COVID-19 condition (identified by ICD-10 code), all-cause emergency department (ED) visits, hospitalization, and death during the follow-up period (90–180 days) after the diagnosis of COVID-19.

**Results** From an initial recruitment of 42,674 non-hospitalized patients with COVID-19 and known 25(OH)D status, a VDD group of 8300 was identified and propensity matched with 8300 controls. During the follow-up period, the VDD group had a higher risk of the primary outcome than did the control group [hazard ratio (HR) = 1.122; 95% confidence interval (CI) = 1.041–1.210]. The VDD group also had a higher risk of all-cause ED visits (HR = 1.114; 95% CI = 1.012–1.226), all-cause hospitalization (HR = 1.230; 95% CI = 1.105–1.369), and all-cause death (HR = 1.748; 95% CI = 1.047–2.290) but not post-COVID-19 condition (HR = 0.980; 95% CI = 0.630–1.523), individually.

**Conclusion** Among the COVID-19 patients, VDD might be associated with a higher risk of all-cause ED visits, hospitalization, and death during the post-acute phase.

**Keywords** Post-COVID-19 condition · Long COVID · SARS-CoV-2 · Vitamin D · Hospitalization · Mortality

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## Introduction

Coronavirus disease 2019 (COVID-19) is a rapidly spreading infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1] that can induce severe inflammation and life-threatening complications [2]. As of June 19, 2023, more than 767,984,989 confirmed cases and 6,943,390 related deaths were reported worldwide [1]. Patients who survive the acute phase of COVID-19 still have a high risk of all-cause mortality and clinical sequelae during their post-acute phase of infection [3, 4]. Previous studies have shown that approximately 10% of patients infected with SARS-CoV-2 may develop post-COVID-19 condition, which is commonly known as long COVID [5–7]. Post-COVID-19 condition is characterized by new or persistent symptoms that typically occur within 3 months from the onset of acute infection, last for at least 2 months, and can affect almost every organ system [7, 8]. Its clinical manifestations range from general symptoms, such as fatigue and weakness, to neuropsychiatric deficits, including cognitive dysfunction or "brain fog" [7]. Despite the rapidly escalating global burden of post-COVID-19 condition, its prevention and treatment strategies remain unclear.

Vitamin D, a fat-soluble secosteroid hormone, plays an important role in modulating the immune system and combating viral infections [9–11]. Several studies have reported that adequate levels of serum 25-hydroxyvitamin D might enhance the immune response against viral infections [10, 12, 13]. Notably, vitamin D deficiency (VDD), defined as serum 25-hydroxyvitamin D levels < 20 ng/mL [14–16], can undermine these beneficial immunological effects [11, 17]. The prevalence of VDD has consistently remained high, at approximately 47.9%, from 2000 to 2022 [18]. Furthermore, it is even higher among patients with COVID-19, at 54% [19], reaching 84% among patients with post-COVID-19 condition [20].

A study demonstrated that patients with post-COVID-19 condition tend to exhibit lower 25-hydroxyvitamin D levels than do those without this condition [21]. However, these findings may be influenced by potential confounding factors such as pre-existing metabolic disorders, vaccination status, and variations in the SARS-CoV-2 virus [22]. Therefore, the present global comparative retrospective study aimed to explore the potential association between VDD and the post-acute outcomes of SARS-CoV-2 infection.

## Methods

### Data source

This retrospective study was conducted to determine the association between VDD and the risk of post-acute outcomes of COVID-19 using TriNetX research network data from January to November 2022. TriNetX is a collaborative global health platform that collects real-time electronic medical data of 117 million individuals from 110 healthcare organizations (HCOs) across 14 countries and reports only aggregated and de-identified population-level data. This data source is widely recognized and has been effectively used to study various globally relevant medical topics, including COVID-19 [23–28]. As individual identities remain unidentifiable in the TriNetX reports, the need for written informed consent was waived for this study [29]. This study was approved by the institutional review board of the Chi Mei Medical Center (approval no. 11202–002).

### Selection of study participants

The inclusion criteria were patients who (a) were aged ≥ 18 years; (b) had a positive polymerase chain reaction test result for COVID-19 (laboratory test with the TNX:LAB:9088 code) or were diagnosed with COVID-19 (an International Classification of Diseases, Tenth Revision [ICD-10], Clinical Modification code of U07.1) for the first time, as previously described [30, 31]; (c) underwent a laboratory test for the serum or plasma 25-hydroxyvitamin D level (laboratory test with the TNX:LAB:9034 code) within 3 months prior to the SARS-CoV-2 infection; and (d) had visited HCOs at least twice between January 1 and November 30, 2022.

The enrolled patients were categorized into two groups on the basis of their vitamin D status. The study group (VDD group) had VDD, defined as 25-hydroxyvitamin D levels < 20 ng/mL (= 50 mmol/L), whereas, the control group had vitamin D levels ≥ 20 ng/mL [32].

To ensure similar disease severity between the two groups, patients who required hospitalization or an emergency department (ED) visit within 7 days of SARS-CoV-2 infection; died within 3 months of SARS-CoV-2 infection; or were undergoing antiviral treatment with agents such as ritonavir plus nirmatrelvir, remdesivir, or molnupiravir were excluded.

### Covariates

The VDD and control groups were created using the following 1:1 propensity score matching (PSM) variables: (a)

demographics (age, sex, and race); (b) social determinants of adverse health outcomes (problems related to housing and economic circumstances, education and literacy, employment and unemployment, and occupational exposure to risk factors); and (c) comorbidities (overweight and obesity, malnutrition, nicotine dependence, alcohol-related disorders, hypertension, hyperlipidemia, diabetes mellitus, neoplasms, chronic lower respiratory tract diseases, liver disease, chronic kidney disease, end-stage renal disease, cerebrovascular disease, heart failure, atrial fibrillation and flutter, and ischemic heart disease)(supplemental Table 1 and 2).

### Outcomes

The primary outcome was a composite of post-COVID-19 condition (identified by ICD-10 code—[U09]), all-cause ED visits, all-cause hospitalization, and all-cause death. The secondary outcomes were post-COVID-19 condition, all-cause ED visits, all-cause hospitalization, and all-cause death, individually. These outcomes were observed during the follow-up period, spanning 90 days after the initial SARS-CoV-2 infection and extending to the end of the follow-up period at 180 days (supplemental Table 1). To ensure that all patients had been followed up for more than 180 days, we restricted our inclusion criteria to patients diagnosed with COVID-19 on or before November 30, 2022.

### Statistical analyses

All statistical analyses were performed using the built-in functions of the TriNetX platform. The characteristics of the two groups are presented as mean ± standard deviation (SD) or frequency and proportion. PSM was performed to balance the covariate distribution between the two groups at baseline by employing a nearest-neighbor greedy matching algorithm with a caliper width of 0.1 pooled SDs. Any variable exhibiting a standardized difference < 0.1 between the two groups indicated adequate matching [33]. After matching, Kaplan–Meier analyses coupled with log-rank tests were used to estimate the incidence of each outcome. The results are expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). The threshold for statistical significance was set at $p < 0.05$. Subgroup analyses were performed according to age, sex, vitamin D status [15], and vaccine dose.

## Results

### Demographic characteristics of the enrolled patients

This study enrolled 42,674 non-hospitalized patients with COVID-19, all of whom underwent 25-hydroxyvitamin D testing. These patients were identified from 110 HCOs across 14 countries in the TriNetX network on June 19, 2023 (Fig. 1). Among them, 8350 (19.6%) were categorized into the VDD group and the remaining 34,324 (80.4%) patients into the control group (Table 1). Before matching, significant differences were observed between the two groups. The VDD group was younger than the control group (49.4 ± 17.6 years vs. 54.9 ± 17.3 years, respectively). The VDD group had a higher proportion of males than the control group (33.9% vs. 28.5%). The VDD group had a lower proportion of individuals identifying as White, Native Hawaiian or Other Pacific Islander, and unknown race (36.1% vs. 62.8%, 38.3% vs. 44.1%, and 39.9% vs. 23.5%, respectively) and a higher proportion of individuals identifying as Black or African American (20.3% vs. 10.3%, respectively). In addition, the VDD group exhibited a higher prevalence of alcohol-related disorders and nicotine dependence but lower rates of hypertension, hyperlipidemia, and neoplasms. After matching, each group had 8,300 patients with balanced baseline characteristics (all standardized differences < 0.1) (Table 1).

### Primary and secondary outcomes

During the follow-up period of 90–180 days after COVID-19 diagnosis, the composite primary outcome was reported in 1,426 (17.2%) patients in the VDD group and 1,295 (15.6%) in the control group (HR = 1.122; 95% CI = 1.041–1.210; Table 2). Furthermore, patients with VDD exhibited a higher cumulative curve of event probability within 90–180 days, indicating a significantly higher incidence of the composite primary outcome than that of the control group (log-rank test, $p < 0.0001$; Fig. 2A). In contrast, the risk of post-COVID-19 condition was similar between groups (HR = 0.980; 95% CI = 0.630–1.523 in Table 2 and log-rank test, $p = 0.9275$; Fig. 2B). The VDD group showed a significantly higher risk of all-cause ED visits (HR = 1.114; 95% CI = 1.012–1.226), all-cause hospitalization (HR = 1.230; 95% CI = 1.105–1.369), and all-cause death (HR = 1.748; 95% CI = 1.047–2.290) than did the control group, except for post-COVID-19 condition (HR = 0.980; 95% CI = 0.630–1.523; Table 2). Lastly, the VDD group showed a significantly higher risk of composite outcome of all-cause ED visits, hospitalization or death (log-rank test, $p = 0.0180$; Fig. 2C).

### Subgroup analysis

Regarding the primary outcome, the VDD group was at a higher risk across most subgroups: sex, age, unvaccinated status, 25-hydroxyvitamin D level (Fig. 3A). However, a non-significantly higher risk of the primary outcome in the VDD group was observed in the subgroup that received both

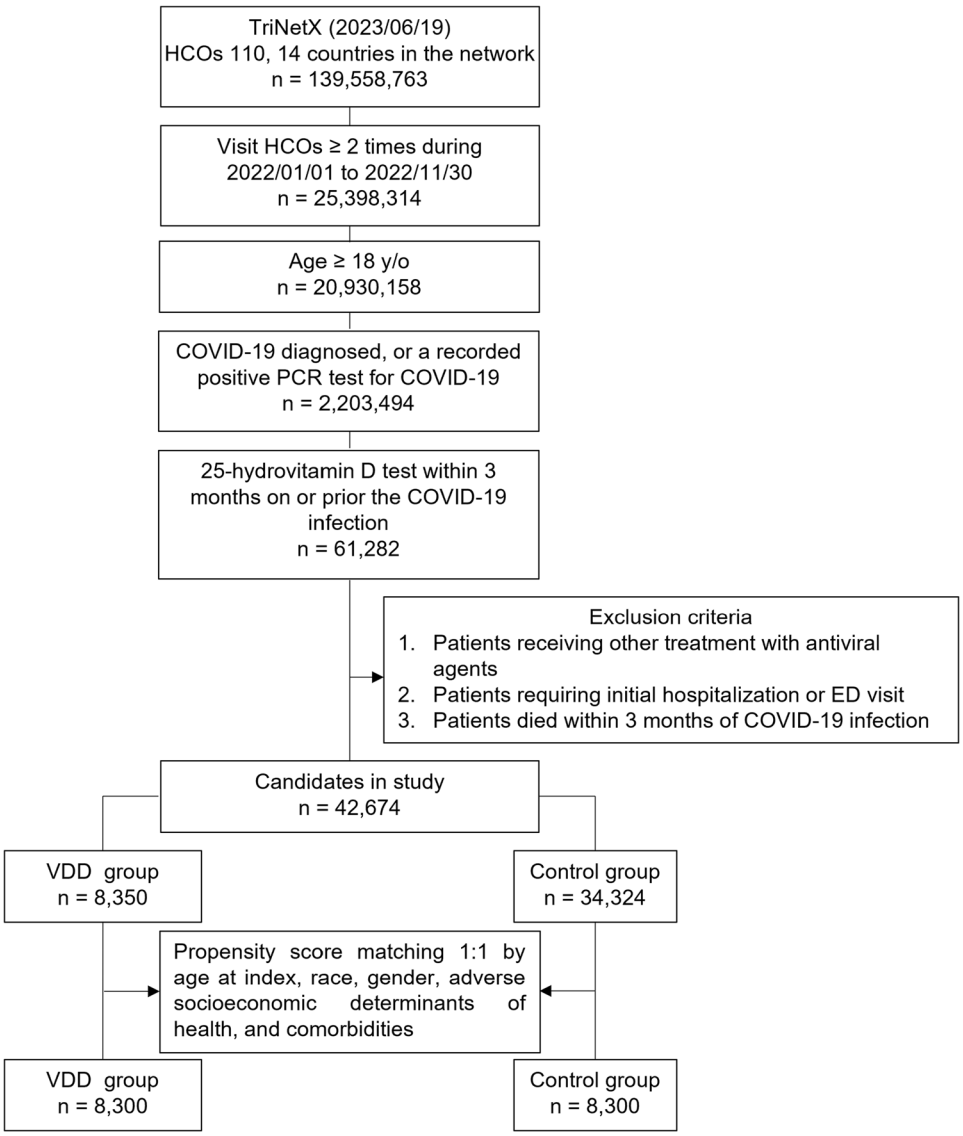


**Fig. 1** Flowchart of patient selection. *COVID-19* coronavirus disease 2019, *ED* emergency department, *HCOs* healthcare organizations, *PCR* polymerase chain reaction, *y/o* years old, *VDD* vitamin D deficiency

vaccines (Fig. 3A). In terms of the secondary outcomes, similar non-significant results for the risk of post-COVID-19 condition were observed in all subgroups (Fig. 3B). A significantly higher risk of all-cause hospitalization was also observed in most subgroups of patients with VDD, except for those who received two or ≥ three vaccines (Fig. 3B). For all-cause ED visits, significant differences were observed only in those who were unvaccinated or received ≥ three vaccines. As for all-cause death, a significantly higher risk was observed in patients with VDD in the following subgroups: male sex, age ≥ 65 years, and, 25-hydroxyvitamin D levels between 12 and 20 ng/mL (Fig. 3B).

## Discussion

This large retrospective study involving 16,600 patients with COVID-19 focused on examining the relationship between VDD and the risk of post-acute outcomes of SARS-CoV-2 infection. VDD was associated with a higher risk of post-acute outcomes of COVID-19, which is supported by the following evidence. Since post-COVID-19 conditions and clinical outcomes such as ED visits, hospitalizations, and mortality are the most significant concerns for patients who have survived acute COVID-19, this

**Table 1** Baseline characteristics of the study population before and after propensity score matching

| Variables | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | VDD group ($n=8,350$) | Control group ($n=34,324$) | Std diff | VDD group ($n=8,300$) | Control group ($n=8,300$) | Std diff |
| Age at index, years | | | | | | |
| Mean ± SD | 49.4 ± 17.6 | 54.9 ± 17.3 | 0.3137 | 49.5 ± 17.6 | 49.4 ± 17.2 | 0.0058 |
| Sex, *n* (%) | | | | | | |
| Female | 5522 (66.1) | 24,544 (71.5) | 0.1162 | 5509 (66.4) | 5517 (66.5) | 0.0020 |
| Male | 2828 (33.9) | 9776 (28.5) | 0.1165 | 2791 (33.6) | 2781 (33.5) | 0.0026 |
| Race, *n* (%) | | | | | | |
| White | 3018 (36.1) | 21,568 (62.8) | 0.5540 | 3017 (36.3) | 3040 (36.6) | 0.0058 |
| American Indian or Alaska Native | 44 (0.5) | 103 (0.3) | 0.0354 | 44 (0.5) | 44 (0.5) | 0 |
| Native Hawaiian or other Pacific Islander | 3194 (38.3) | 15,130 (44.1) | 0.1186 | 3165 (38.1) | 3192 (38.5) | 0.0070 |
| Black or African American | 1696 (20.3) | 3540 (10.3) | 0.2804 | 1664 (20) | 1724 (20.8) | 0.0179 |
| Asian | 243 (2.9) | 1,022 (3) | 0.0040 | 243 (2.9) | 251 (3) | 0.0057 |
| Unknown race | 3332 (39.9) | 8052 (23.5) | 0.3591 | 3315 (39.9) | 3223 (38.8) | 0.0227 |
| Social determinants of health associated with adverse outcomes, *n* (%) | | | | | | |
| Problems related to housing and economic circumstances | 217 (2.6) | 370 (1.1) | 0.1134 | 195 (2.3) | 170 (2) | 0.0205 |
| Problems related to employment and unemployment | 92 (1.1) | 343 (1) | 0.0100 | 91 (1.1) | 101 (1.2) | 0.0113 |
| Problems related to education and literacy | 15 (0.2) | 46 (0.1) | 0.0115 | 14 (0.2) | 10 (0.1) | 0.0127 |
| Occupational exposure to risk factors | 10 (0.1) | 32 (0.1) | 0.0081 | 10 (0.1) | 10 (0.1) | 0 |
| Comorbidities, *n* (%) | | | | | | |
| Overweight and obesity | 2462 (29.5) | 9354 (27.3) | 0.0496 | 2440 (29.4) | 2527 (30.4) | 0.0229 |
| Malnutrition | 437 (5.2) | 1349 (3.9) | 0.0624 | 423 (5.1) | 444 (5.3) | 0.0114 |
| Alcohol-related disorders | 423 (5.1) | 1029 (3) | 0.1053 | 400 (4.8) | 365 (4.4) | 0.0201 |
| Nicotine dependence | 952 (11.4) | 2723 (7.9) | 0.1176 | 919 (11.1) | 899 (10.8) | 0.0077 |
| Essential (primary) hypertension | 3194 (38.3) | 15,130 (44.1) | 0.1186 | 3165 (38.1) | 3192 (38.5) | 0.0067 |
| Disorders of lipoprotein metabolism and other lipidemias | 2510 (30.1) | 14,759 (43) | 0.2712 | 2498 (30.1) | 2401 (28.9) | 0.0256 |
| Diabetes mellitus | 1990 (23.8) | 7494 (21.8) | 0.0476 | 1957 (23.6) | 1974 (23.8) | 0.0048 |
| Neoplasms | 1985 (23.8) | 11,496 (33.5) | 0.2163 | 1979 (23.8) | 1988 (24) | 0.0025 |
| Chronic lower respiratory diseases | 1710 (20.5) | 7616 (22.2) | 0.0417 | 1688 (20.3) | 1,715 (20.7) | 0.0081 |
| Liver diseases | 1022 (12.2) | 3820 (11.1) | 0.0346 | 1002 (12.1) | 987 (11.9) | 0.0056 |
| Chronic kidney disease | 1275 (15.3) | 4967 (14.5) | 0.0224 | 1249 (15) | 1246 (15) | 0.0010 |
| End stage renal disease | 439 (5.3) | 1142 (3.3) | 0.0953 | 426 (5.1) | 447 (5.4) | 0.0113 |
| Cerebrovascular diseases | 666 (8) | 2862 (8.3) | 0.0132 | 652 (7.9) | 621 (7.5) | 0.0140 |
| Heart failure | 776 (9.3) | 2,570 (7.5) | 0.0652 | 751 (9) | 736 (8.9) | 0.0063 |
| Atrial fibrillation and flutter | 506 (6.1) | 2376 (6.9) | 0.0350 | 498 (6) | 489 (5.9) | 0.0046 |
| Ischemic heart diseases | 1002 (12) | 4730 (13.8) | 0.0532 | 985 (11.9) | 913 (11) | 0.0273 |

*SD* standard deviation, *Std diff* standardized difference, *VDD* vitamin D deficiency

study employed a composite outcome comprising these indicators as the primary point of interest. First, following SARS-CoV-2 infection, patients with VDD exhibited a significantly increased risk of the primary outcome—a composite of post-COVID-19 condition, all-cause ED visits, hospitalization, and death. Second, consistent primary effects were observed across subgroups stratified by sex, age, and 25-hydroxyvitamin D levels. Finally, during the follow-up period, the VDD group had a higher risk of the individual outcomes of all-cause ED visits, hospitalization, and death. However, no significant difference between the two groups regarding the individual outcome of post-COVID-19 condition during the follow-up period was identified. These findings indicate that VDD may be associated with a higher risk of post-acute outcome of SARS-CoV-2 infection. Further studies are warranted to investigate whether vitamin D supply would reverse this phenomenon.

Previous studies [34–37] have demonstrated a significant association between 25-hydroxyvitamin D levels and clinical outcomes of acute SARS-CoV-2 infection. A single-centered study identified that patients with deficient

**Table 2** Hazard ratio of primary and secondary outcomes for the matched vitamin D deficiency group and the control group

| Outcomes | Patients with outcome | | Hazard ratio (95% CI) | *p* value |
|---|---|---|---|---|
| | VDD group | Control group | | |
| Primary outcome | | | | |
| Development post-COVID-19 condition, all-cause ED visits, hospitalization, or death | 1,426 | 1,295 | 1.122 (1.041–1.210) | **0.0027** |
| Secondary outcomes | | | | |
| Development of post-COVID-19 condition | 39 | 40 | 0.980 (0.630–1.523) | 0.9275 |
| All-cause ED visits | 879 | 798 | 1.114 (1.012–1.226) | **0.0268** |
| All-cause hospitalization | 742 | 613 | 1.230 (1.105–1.369) | **< 0.0001** |
| All-cause death | 40 | 23 | 1.748 (1.047–2.920) | **0.0306** |

*CI* confidence interval, *COVID-19* coronavirus disease 2019, *ED* emergency department, *VDD* vitamin D deficiency

25-hydroxyvitamin D levels had higher all-cause 30-day mortality than did those with sufficient levels (32.1% vs. 13.8%, respectively) [34]. A multinational study has shown a positive correlation between VDD and SARS-CoV-2 infection ($r = 0.55$, $p = 0.01$, $R^2 = 0.31$) and mortality ($r = 0.50$, $p = 0.01$, $R^2 = 0.25$) [35]. Furthermore, a systematic review and meta-analysis of observation studies by Mehri et al. [36] reported that patients with COVID-19 and VDD were associated with higher mortality [five studies: odds ratio (OR) = 2.64; 95% CI = 1.86–3.76; two studies: HR = 1.86; 95% CI = 1.38–2.51]. In addition, Jude et al. [37] reported that participants with COVID-19 and VDD had a higher risk of hospitalization (OR = 2.33; 95% CI = 1.98–2.74). While previous studies provided valuable insights, they often lacked the long-term follow-up period to clarify how VDD associated with post-acute outcomes of COVID-19. In this study, the negative impact of VDD was not only observed in the acute phase of COVID-19 but also in the post-acute phase of SARS-CoV-2 infection.

The underlying mechanisms linking VDD to adverse clinical outcomes in patients with COVID-19 are still under investigation. At present, several plausible theories have been proposed. First, VDD may lead to immune dysregulation, resulting in dysregulated cytokine production and an exaggerated inflammatory response that contribute to more severe disease outcomes [38, 39]. Second, the angiotensin-converting enzyme 2 (ACE2) receptor has been identified as the primary cellular entry point of SARS-CoV-2 [40]. VDD can upregulate *ACE2* expression, increasing susceptibility to viral entry and subsequent viral replication, thereby exacerbating the severity of COVID-19 [41]. These hypotheses may provide plausible explanations for patients with COVID-19 and VDD experiencing increased adverse clinical outcomes.

VDD arises from the complex interplay among various factors that affect vitamin D synthesis, absorption, and metabolism [42–45]. Recently, the reported prevalence of VDD has increased with the frequency of vitamin D testing [46]. It is a global issue, with many countries reporting prevalence rates of > 20% [47, 48]. The prevalence of VDD varies between countries, with a range of 20%–40% [47, 49, 50]. In the context of COVID-19, Kalichuran et al. [51] reported that symptomatic patients have a higher prevalence of VDD than do asymptomatic patients. Among the COVID-19 population, the prevalence of VDD is reportedly as high as 54% [19], and reaching up to 84% in patients with post-COVID-19 condition [20]. This indicates that the severity of COVID-19 may be a substantial factor associated with VDD. In the pre-matched subjeccts, a VDD prevalence of approximately 20% was found in the enrolled population. This estimate is lower than those of previous studies, which might be due to the relatively mild severity of the disease in the selected patients. Patients who received antiviral drugs and those who died within 3 months of the indexed date were excluded. Hence, the actual prevalence of VDD could have been underestimated in this study.

This study had several strengths. First, in this large retrospective study, which focused on the SARS-CoV-2 Omicron variant outbreak in 2022, the results were particularly relevant to the current situation. Second, robust statistical methods such as PSM were used to control for confounding variables and biases. Finally, real-world data from electronic health records were used, which reflected the true complexity and heterogeneity of patients, making the results more applicable in real-world settings.

This study also had some limitations. First, the TriNetX database primarily encompasses data from individuals who have sought medical care within healthcare systems, thereby potentially excluding certain population subsets such as individuals residing in rural areas, healthy individuals who do not frequently seek medical care, or undocumented immigrants. Therefore, the findings may not be representative of a larger population. Second, to control disease severity and heterogeneity, hospitalized patients, and those using antiviral drugs were excluded. The study period was set to be after 2022, during the

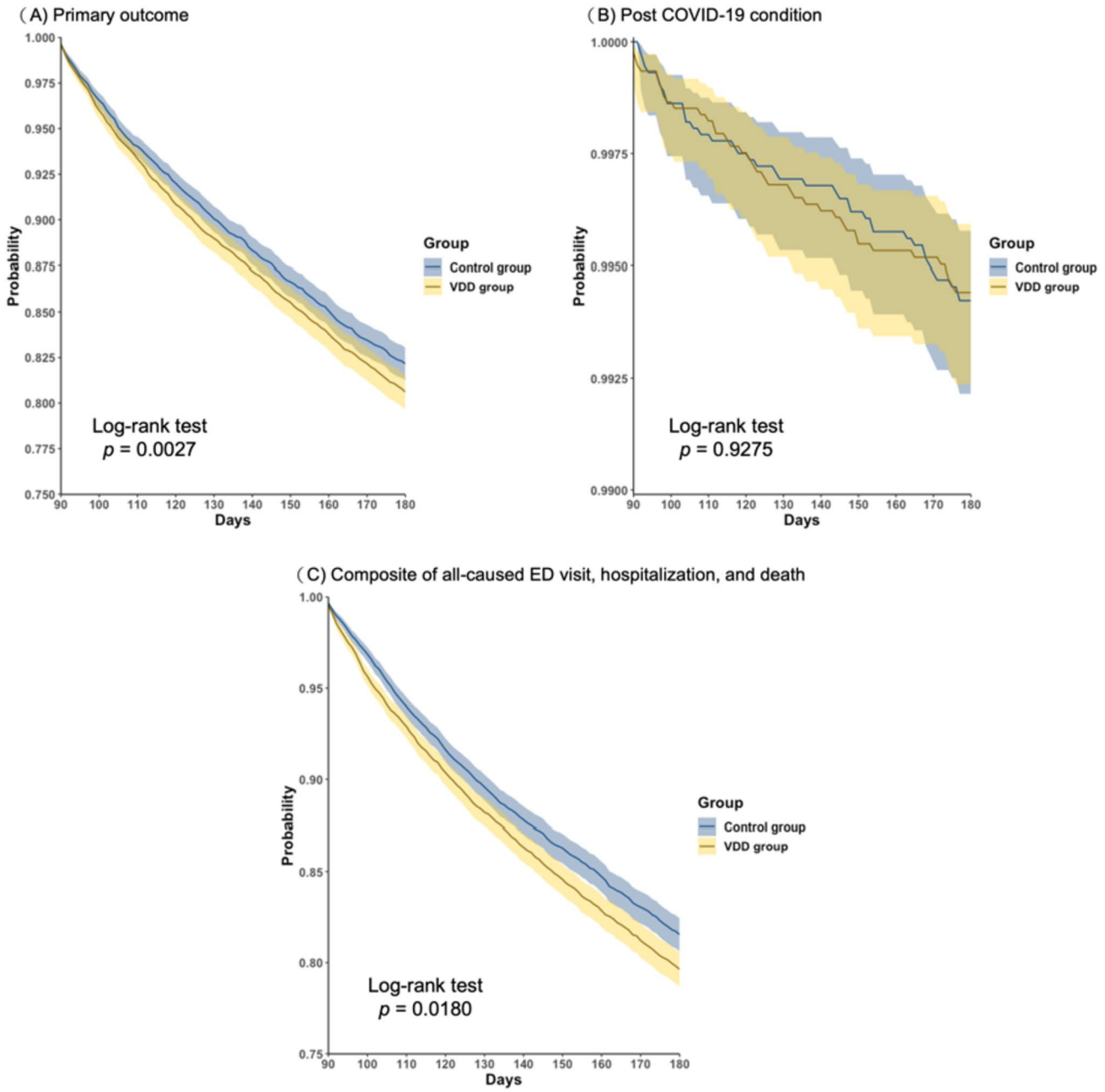


**Fig. 2** Kaplan–Meier curves for time-to-event free of the outcome: (**A**) the primary outcome: a composite of development of post COVID-19 condition, all-cause emergency department (ED) visits, hospitalization, and death; (**B**) post COVID-19 condition; (**C**) a composite of all-cause ED visit, hospitalization, and death. VDD, vitamin D deficiency

Omicron wave. This may limit the extent of the generalizability of the findings. The results of this study may not be directly applicable to patients with more severe forms of the disease, treated with antiviral drugs, or infected with different viral strains during different periods of the pandemic. Third, although PSM was employed to balance the numerous baseline differences between the two groups, certain factors, including food intake, dietary supplements, and sun exposure time, the timing of vitamin D measurement, and the post-COVID-19 vitamin level, could not be accounted for in the analysis. Finally, it is worth noting that the prevalence of post-COVID-19 conditions in this study is notably lower than what was reported in a previous study [52]. This disparity could be attributed to the fact that this study relied on ICD-10 codes for the identification of post-COVID-19 conditions, which might result in underreporting compared to more comprehensive assessment methods.

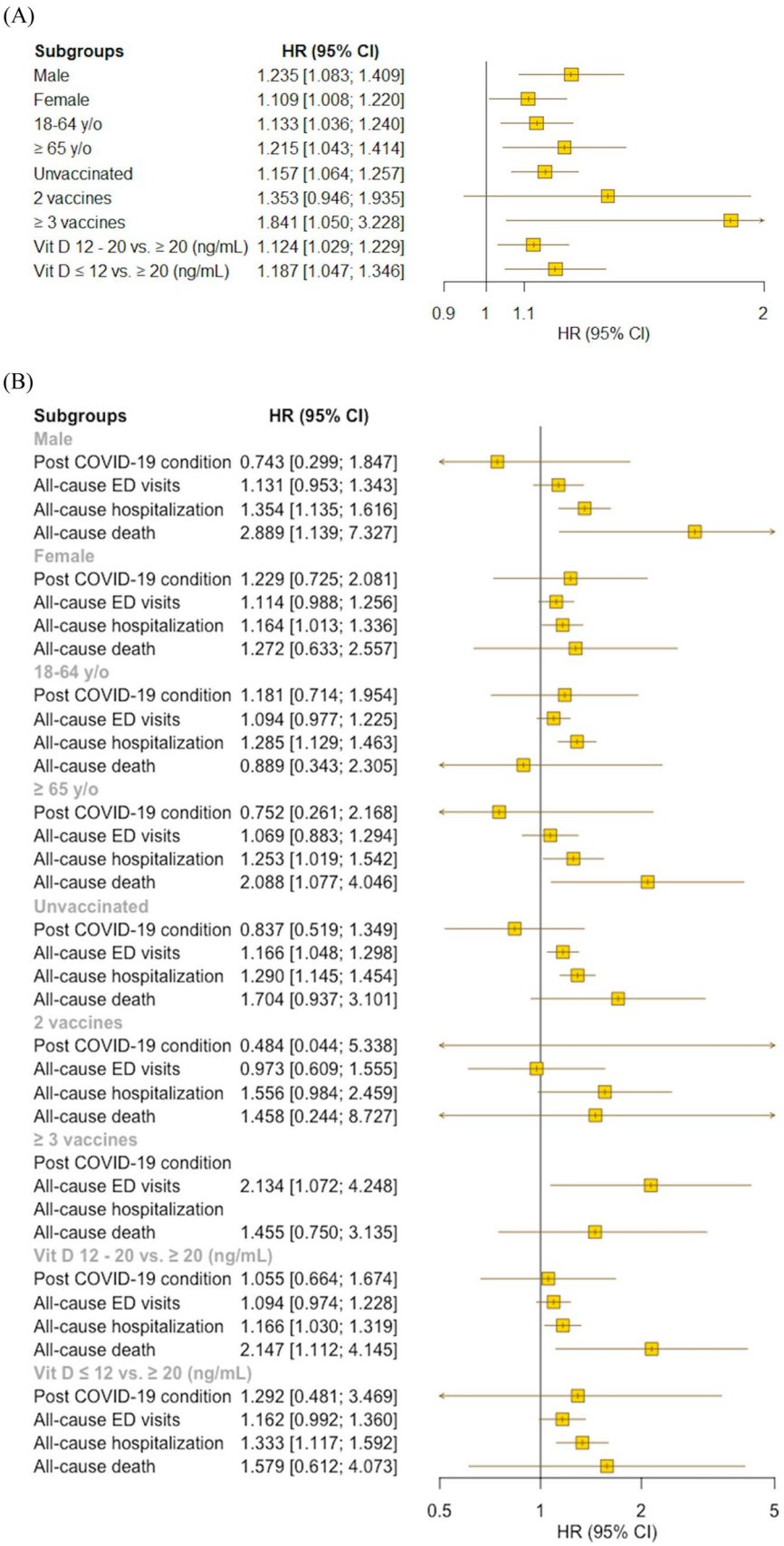


**Fig. 3** Subgroup analyses of (**A**) the primary outcome and (**B**) secondary outcomes for the matched vitamin D deficiency group and the control group. *CI* confidence interval, *COVID-19* coronavirus disease 2019, *ED* emergency department, *HR* hazard ratio, *y/o* years old, *Vit D* serum 25-hydroxyvitamin D

## Conclusion

Among non-hospitalized patients, VDD might be one of risk factors for post-acute outcomes of SARS-CoV-2 infection, potentially associated with adverse clinical outcomes such as ED visits, hospitalization, and death during the follow-up period of 90–180 days.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00394-023-03298-3.

**Author contributions** J-YW conceptualized, designed the study performed the data analysis and drafted the manuscript. M-YL, W-HH, Y-WT, T-HL, P-YH, M-HC, and S-EC assisted data collection and created figures. M-YL and C-CL contributed to project design and edited the manuscript. J-YW was responsible for the data interpretation. C-CL finalized the manuscript. All authors approved the final version of the manuscript.

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**Data availability** The findings of this study are available on request from the corresponding author.

**Declaration**

**Conflict of interest** The authors declare that there is no conflict of interests.

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