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Ivin Kuriakose
Clinical Nurse Manager 2, Our Lady of Lourdes Hospital, Drogheda, Ireland

Comfort Chima
Nurse Tutor, School of Nursing and Midwifery, RCSI, Dublin, Ireland

Corresponding Author:
Ivin Kuriakose
Clinical Nurse Manager 2, Our Lady of Lourdes Hospital, Drogheda, Ireland

What is the impact of vitamin D supplementation on the survival rate of COVID-19 in adult patients?

Ivin Kuriakose and Comfort Chima

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Abstract
Reports suggest that administering vitamin D supplements in low doses typically between 10µg and 25µg per day can provide effective protection against respiratory infections. ACE 2 receptor proteins tend to bind with corona viruses in the infection process and, more importantly, vitamin D can disrupt the ACE 2 receptor protein's path. This means that vitamin D supplementation can have consequences on survival rates in COVID-19 patients.

Methodology: A systematic review was conducted using a narrative synthesis approach to examine studies related to the research question. Data sources for this review included BMJ journals, CINAHL Plus with full text, the Cochrane Library, PubMed, Medline, and Research Gate. The review process followed the PICO (Population, Intervention, Comparison, Outcome) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure a structured and transparent approach. After screening 980 studies, only seven met the full inclusion criteria. Data extraction was carried out using Microsoft Excel 2019, and the analysis of the selected studies was performed using a narrative synthesis approach, which allowed for the organization and summarization of key findings without statistical pooling. This approach helped to identify trends and insights from the data while highlighting the context and limitations of the studies.

Results: The seven studies included in this research accounted for a total of 663 COVID-19 patients. All studies assessed the primary outcome 'survival rate' among its participants reported rates as high as 100% to as low as 81.25%. Three studies assessed clinical outcomes in reference to the World Health Organization's Ordinal Scale for Clinical Improvement (OSCI) score for COVID-19 and all reported significant decreases in the score following vitamin D supplementation. There were also significantly lower rates of admission to the ICU.

Conclusion: The findings of this review suggest that clinicians should consider vitamin D supplementation for adult COVID-19 patients admitted to their facilities.

Keywords: Vitamin D, supplementation, survival rate, COVID-19, adult patients

Introduction
COVID-19, caused by the SARS-CoV-2 virus, emerged in late 2019 and was declared a global pandemic by the World Health Organization (WHO) in March 2020 due to its rapid global spread. As of 2021, there have been over 230 million confirmed cases and over 4.7 million deaths worldwide (WHO, 2021) [1]. In Europe, over 69 million people have been affected, and in Ireland, the confirmed cases stand at 380,720 with 5,209 deaths (WHO, 2021) [1]. Given the widespread nature of the disease, it is critical to explore preventive and therapeutic measures to reduce the impact of COVID-19.

One promising intervention under investigation is vitamin D supplementation. Research has suggested that vitamin D, particularly in doses between 10µg and 25µg per day, can help prevent respiratory infections, potentially providing protection against COVID-19 (Anand *et al*., 2021; Cuadrado-Payán *et al*., 2020; Fabbri *et al*., 2020; Song *et al*., 2020) [12, 13, 15]. Vitamin D is thought to influence the immune system by interacting with the ACE 2 receptor, which the virus uses to enter cells (Song *et al*., 2020; Morawska & Milton, 2020) [15, 16]. Furthermore, it is believed that vitamin D may reduce cytokine production, preventing the dangerous cytokine storm that contributes to severe COVID-19 outcomes, such as acute respiratory distress syndrome (ARDS) and multi-organ failure (Sabico *et al*., 2021; Lao *et al*., 2021) [10].

Several studies, including randomized controlled trials (RCTs) and quasi-experimental research, have explored the effects of vitamin D supplementation in COVID-19 patients, particularly adults (Annweiler *et al*., 2020a; Castillo *et al*., 2020; Murai *et al*., 2021) [1, 7, 9].

These studies suggest that vitamin D may have a role in reducing the severity of infections and improving survival rates, especially by modulating immune responses. Given these findings, further research into vitamin D supplementation during the COVID-19 pandemic could yield valuable clinical recommendations for managing and preventing severe cases [3].

Rational of review

The COVID-19 pandemic has underscored the need for effective treatments to reduce severity and mortality. While vaccines have been effective, adjunctive treatments like vitamin D supplementation are gaining attention for their potential to improve outcomes. Vitamin D plays a key role in regulating the immune system, potentially modulating inflammatory responses and enhancing defenses against respiratory infections. Studies suggest low vitamin D levels may increase susceptibility to infections, including COVID-19, and influence the ACE2 receptor, which SARS-CoV-2 uses to enter cells. Additionally, vitamin D may help reduce excessive cytokine production, which is linked to severe complications like ARDS. Preliminary studies have shown promising results, but findings remain mixed. A systematic review is needed to assess the impact of vitamin D supplementation on survival rates in adult COVID-19 patients and provide clinical guidance [4].

Methodology

A methodologically structured approach is crucial for conducting a high-quality, non-biased systematic review (SR), which allows for accurate analysis of the impact of vitamin D supplementation on the survival rates of COVID-19 patients. Following the guidance of experts in systematic reviews (Khan *et al*., 2003; Renjith *et al*., 2015; Caldwell & Bennett, 2020) [17, 18, 19], the review was designed to address specific outcomes and criteria that ensure the relevance and rigor of the findings.

The primary outcome of the review is the survival rate of COVID-19 patients receiving vitamin D supplementation, while secondary outcomes include mortality, the duration of vitamin D supplementation, and the number of patients admitted to intensive care units. A clear and structured search strategy, including the use of key terms and MESH headings, was employed to identify relevant studies. Databases like PubMed, CINAHL, and Cochrane Library, along with grey literature sources such as Google Scholar and DynaMed, were systematically explored. The search was limited to English-language studies published from 2019 onwards, with no unpublished studies included. The review followed the PRISMA guidelines, and a PRISMA flow diagram was used to track the screening process.

Inclusion and exclusion criteria, derived from the PICO question, were rigorously defined to ensure that only studies focusing on adult patients with COVID-19 receiving vitamin D supplementation in hospital or residential care settings were included. Non-peer-reviewed articles, studies in languages other than English, and studies focusing on other respiratory diseases or inappropriate designs were excluded. A data extraction table was used to collect relevant information, including study details, sample characteristics, and outcomes. Data extraction was carried out by one reviewer and verified by a second reviewer to ensure accuracy.

For data analysis, a narrative synthesis approach was adopted, complemented by MS Excel for further analysis. The quality of included studies was assessed using the Evidence-Based Librarianship (EBL) tool, which evaluates study validity, applicability, and appropriateness through a set of critical questions. This process ensures that only high-quality studies contribute to the synthesis, ultimately providing reliable evidence regarding the role of vitamin D supplementation in improving survival rates in COVID-19 patients.

Exclusion of 21 studies was due to various reasons, including ongoing studies, inappropriate designs, language barriers, and lack of relevant findings. The final set of seven studies, published between 2020 and 2022, provided contemporary and time-relevant findings, with studies conducted in diverse global settings. The analysis of these studies allowed for a comprehensive understanding of the potential benefits of vitamin D supplementation in improving COVID-19 outcomes.

Discussion

The purpose of this review was to examine the effects of vitamin D supplementation on the clinical outcomes of COVID-19 patients, particularly focusing on mortality rate, disease severity, and the need for intensive care. Seven studies involving a total of 663 COVID-19 patients were analyzed, and the results indicated that vitamin D supplementation had a positive impact on reducing mortality, improving survival rates, and lowering clinical complications such as ICU admissions. Additionally, supplementation helped reduce serum levels of inflammatory markers, suggesting a potential role in mitigating the inflammatory response associated with severe COVID-19.

Vitamin D is known for its immunological properties, including its influence on the Renin-Angiotensin-Aldosterone-System, immune regulation, and its antiviral, anti-inflammatory, and antioxidant effects. Several studies (Annweiler *et al*. 2020a, Annweiler *et al*. 2020b, Sabico *et al*. 2021) [3, 4, 10] have previously explored the impact of vitamin D on viral and bacterial infections like influenza, HIV, and respiratory syncytial virus, with mixed results. While some studies, such as Annweiler *et al*. (2020a) [3], found significant benefits of vitamin D in managing respiratory infections, others, like Sabico *et al*. (2021) [10], showed limited effects for influenza. In the context of COVID-19, however, the majority of studies in this review (Castillo *et al*. 2020, Murai *et al*. 2021, Rastogi *et al*. 2022) [7, 9, 11] reported a decrease in mortality rates following vitamin D supplementation, with the pooled analysis indicating a noticeable reduction in mortality.

A consistent finding across all studies was the association between vitamin D deficiency and poor clinical outcomes in COVID-19 patients. Factors like diet, age, and limited sun exposure were identified as primary risk factors for vitamin D deficiency, which could worsen COVID-19 outcomes. Despite these promising findings, the review acknowledges that more research is needed to understand the optimal dosage, duration, and potential side effects of vitamin D supplementation, as COVID-19 remains a novel disease requiring further investigation.

Table 1: Data Extraction Table

Author(s)	Country/ Setting	Study Design	Population	Primary Outcome	Secondary Outcome	Duration of Vitamin D Supplementation	Mortality	EBL score (%)
Annweiler *et al*. (2020a) [3]	France - A middle-sized nursing-home in Rhône	Quasi-experimental	Total 66 Intervention group (*n* = 57; mean 87.7 ± 9.3 years; 79% women) Control group (*n* = 9; mean, 87.7 ± 7.2 years; 67% women)	Mortality	9-point WHO ordinal scale for clinical improvement (OSCI) for COVID-19	Intervention group - 80,000 IU vitamin D3 every 2-3 months Control group - No vitamin D supplementation	17.5% died (82.5% survived) in the intervention group 55.6% died (44.4% survived) in the comparison group	84.62
Annweiler *et al*. (2020b) [4]	France - The geriatric acute care unit of Angers University Hospital	Quasi-experimental - Two intervention groups and one comparison group	77 patients diagnosed with SARS-CoV-2. Group 1 (*n* = 29; mean 88 ± 6 years; 20 females) Group 2 (*n* = 16; mean 85 ± 5 years; 5 females) Group 3 (*n* = 32; mean 88 ± 8 years; 13 female)	14-day mortality	9-point WHO ordinal scale for clinical improvement (OSCI) for COVID-19	Group 1 - Supplemented with vitamin D over the preceding year Group 2 - Supplemented with vitamin D after COVID-19 diagnosis Group 3 - No vitamin D supplementation	2 died in Group 1 3 died in group 2 10 died in group 3 Total 15 died	84.62
Castillo *et al*. (2020) [7]	Spain - Reina Sofía University Hospital	RCT	Total 76 Intervention group (*n* = 50; mean 53.14 ± 10.77 years; 46% females) Control group (*n* = 26; mean 52.77 ± 9.35 years; 18% females)	ICU admission	Deaths	Intervention group - Oral calcifediol (0.266 mg) on day 3 and 7, and then weekly until discharge or ICU admission. Comparison group - No vitamin D supplementation	None died in the intervention group 2 died in the control group	96.15
Annweiler *et al*. (2021) [8]	France - The geriatric acute care unit of Angers University Hospital	Quasi-experimental	Total 95 Intervention group (*n* = 67; mean 87.7 ± 5.4 years; 38 female) Comparison group (*n* = 28; mean 88.6 ± 5.7 years; 8 females)	Three-month all-cause mortality	N/A	Intervention group - Bolus vitamin D3 (i.e., 50,000 IU per month, or 80,000 IU or 100,000 IU or 200,000 IU every 2-3 months), or daily supplementation with 800 IU Comparison group - No vitamin D supplementation	23.9% died in the intervention group (51 patients survived) 46.4% died in the control group (15 survived)	84.62
Murai *et al*. (2021) [9]	Brazil - Clinical Hospital of the School of Medicine of the University of Sao Paulo	RCT	Total 240 Intervention group (*n* = 119; mean 56.5 ± 13.8 years; 49 women) Control group (*n* = 118; mean 56.0 ± 15.0 years; 55 women)	Length of hospital stay	Mortality ICU admissions Patients under mechanical ventilation and time Serum levels of 25(OH)D, creatinine Total calcium C-reactive protein	Intervention group - Single dose of 200000IU of Vitamin D3 Control group - No vitamin D supplementation	7.6% died in the intervention group 5.1% died in the control group	96.15
Sabico *et al*. (2021) [10]	Kingdom of Saudi Arabia (KSA) - Tertiary care hospitals in Riyadh	RCT	Total 69 Intervention group (*n* = 36; mean 46.3 ± 15.2 years; 15 females) Control group (*n* = 33; 53.5 ± 12.3 years; 20 female)	Number of days taken to resolve symptoms	Changes in metabolic profile ICU admission Days of discharge Mortality	Intervention group - 5,000 IU supplementation for 2 weeks Control group - 1,000 IU supplementation for 2 weeks	1 in the control groups (35 survived) None in the control group (all survived)	96.15
Rastogi *et al*. (2022) [11]	India - A tertiary care hospital	RCT	Total 40 Intervention group (*n* = 16; mean 50.0 ± 15 years; 10 female) Control group (*n* = 24; mean 47.5 ± 9.9 years; 10 female)	Participants who turn SARS-CoV-2 negative	Changes in the level of inflammatory markers with treatment	Intervention group - Daily 60,000 IU of cholecalciferol (oral nano-liquid droplets) for 7 days with therapeutic target 25(OH)D>50 ng/ml Control group - 25(OH)D levels were assessed at day 7, and cholecalciferol supplementation was continued for those with 25(OH)D<50 ng/ml in the intervention arm.	None reported	96.15

Conclusion

Since its emergence in China, COVID-19 rapidly became a global pandemic, overwhelming healthcare systems worldwide due to its high mortality rate. In response, urgent research was conducted to identify evidence-based interventions to mitigate the impact of the virus. This systematic review aimed to clarify the effects of vitamin D supplementation on the survival rates of adult COVID-19 patients, based on seven studies that met the inclusion criteria. The findings from these studies consistently indicated that vitamin D supplementation helps reduce mortality, improve survival rates, and enhance the overall prognosis of COVID-19 patients. However, the degree of benefit varied across the studies, and there was no consensus on the exact quantification of vitamin D's effects on patient outcomes.

Despite these variations, this review concluded that vitamin D supplementation can be a valuable intervention for adult COVID-19 patients, irrespective of underlying co-morbidities. The results suggest that clinicians should consider incorporating vitamin D supplementation in the treatment protocols for COVID-19 patients. However, further research is essential to determine the optimal dosage, administration route, and potential side effects of vitamin D, as well as its role in preventing COVID-19 infections, to establish more definitive clinical guidelines.

Bias Assessment

1. 1.Exclusion of non-English studies or different settings may limit result generalizability.
2. Positive outcome studies may be more likely to be published, skewing findings.
3. Differences in study types (e.g., RCTs vs. quasi-experimental) could introduce bias.
4. Uncontrolled factors like age, co-morbidities, and baseline vitamin D levels may affect results.

Limitation

1. Variations in design, sample size, and methodology may hinder consistent conclusions.
2. Most studies focused on short-term outcomes, with limited evidence on long-term effects.
3. Inconsistent control of factors like co-morbidities, baseline vitamin D levels, and other treatments may affect outcomes.

Conflict of Interest

Not available

Financial Support

Not available

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