NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

Medical School

DEPARTMENT OF CLINICAL THERAPEUTICS, HOSPITAL ALEXANDRA

Postgraduate Program

MSc: "Clinical Trials: Design and Conduct"

Director of MSc

Evangelos Terpos, Professor of the Medical School of NKUA

Vitamin D3 and COVID-19: a systematic review of meta-analyses

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Table of Contents

Table of Figures

Tables

Table of Appendixes

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Abbreviations

ACE 2	Angiotensin-converting enzyme 2
ARDS	Adult respiratory distress syndrome
ATG	Angiotensinogen
CHUV	Lausanne University Hospital
SARS-COV-2	Coronavirus disease 2019
CRP	C-reactive protein
D2	Ergocalciferol
D3	Cholecalciferol
EDM	Endocrinology, Diabetology and Metabolism
ES	Effect Size
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
G-CSF	Granulocyte-colony stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Ig	Immunoglobulin
IL	Interleukin
IMs	Interstitial macrophages.
IP10	Interferon inducible protein-10
ICU	Intensive Care Unit
IQR	Interquartile Range
LOS	Length of stay
MECIR	Methodological expectations of Cochrane Intervention Reviews
NKUA	National and Kapodistrian University of Athens
NOS	Newcastle–Ottawa Scale
NSP	Non- Structural Proteins
MAS	Macrophage activation syndrome
MERS	Middle east respiratory syndrome (2012)
MLR	Multiple logistic regression
MODS	Multiple organ dysfunction syndrome

OR	Odd Ratio
PD1	Programmed cell death protein-1
PICOS	Patient, problem or population, intervention, comparison, control or comparison, outcome, study design
RTI	Item Bank Research Triangle Institute Item Bank
RR	Relative Risk
Retro	Retrospective studies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSP	Prospective studies
SARS	Severe acute respiratory Syndrome (2002)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2 (2019)
SD	Standard Deviation
Sg-mRNAs	Sub-genomic mRNAs
TIM3	T-cell immunoglobulin domain and mucin domain-3
TNF	Tumor necrosis factor
TGN	Trans-Golgi Network
UNIL	University of Lausanne
VDD	Vitamin D Deficiency
VDI	Vitamin D Insufficiency
VDSL	Vitamin D Serum Level
WHO	World Health Organization

Abstract

Aim: Accumulating body of evidence suggests a role of vitamin D in the course of coronavirus disease 2019 (COVID-19). However, inconsistency still exists across studies. The primary aim of this systematic review is to analyze the evidence presented in meta-analyses regarding the association between 25(OH) D and the SARS-CoV-2 risk or severity, including admission to intensive care unit (ICU) or mortality. Secondary aim was the effect of supplementation on these outcomes.

Methods: A deep search was conducted using PubMed, EMBASE, Scopus, and Cochrane up to 12 February 2022, including meta-analyses on both observational and interventional studies.
Results: Twenty-nine meta-analyses met the inclusion criteria. Sixteen out of eighteen meta-analyses that examined the association between vitamin D status assessed by 25-hydroxy-vitamin D [25 (OH) D] concentrations and SARS-CoV-2 severity and found a strong association, one found a moderate link, and one did not find an association. Then, eight out of ten meta-analyses found an association between the Serum concentrations of 25 (OH) D and the risk infection of SARS-CoV-2, one found a moderate link, and one did not find any association. Moreover, 11 meta-analyses assessed the effect of vitamin D supplementation on SARS-CoV-2 risk or severity of infection. Eight out of ten meta-analyses identified a positive effect on disease severity, and three out of six with risk of infection.

Conclusions: The meta-analyses show that VDD is associated with greater severity and risk of SARS-CoV-2 infection compared with sufficient vitamin D status. Vitamin D supplementation may reduce the risk of SARS-CoV-2 hospitalization, ICU admission, mortality, and the risk of infection.

Keywords: Vitamin D; 25 (OH) Deficiency/inficeciency; SARS-CoV-2; Severity, Risk of Infection, Supplementations, Meta-Analyses.

Part A– General Part

A. Introduction

Coronavirus disease 2019 (SARS-CoV-2), which was first detected in Wuhan, China in December 2019, rapidly spread throughout most countries around the world, resulting in a global pandemic. Millions of deaths and illnesses have been attributed to COVID-19. Therefore, effective therapeutic strategies to treat or prevent SARS-COV-2infection and avert the progression of SARS-COV-2were developed in order to lower both the mortality rate and the severity of the disease ((Rohilla, 2021). People who have been exposed to SARS-CoV-2 can also strengthen their immune systems to protect themselves from contracting an infection, and they can lower their inflammatory response to protect their organs from deterioration in the event that they develop the disease (Mrityunjaya et al., 2020), (Grant et al., 2020).There is growing evidence that vitamin D status may impact the risk of contracting severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Vitamin D may play a protective role against SARS-COV-2infection by upregulating the immune system and the expression of angiotensin converting enzyme 2 (ACE2) while simultaneously downregulating the renin angiotensin system (RAS) pathway and the cytokine storm. Both ACE2 and RAS are essential factors for SARS-COV-2infection (Cutolo et al., 2020). VDD has been associated with increased risk of infections, such as acute respiratory tract infections, VDD may be also associated with increased risk and severity of SARS-CoV-2. However, heterogeneity among studies exists with regard to vitamin D supplementation in this regard.

The purpose of this systematic review was to collect and synthesize data from meta-analyses regarding the association between vitamin D status and clinical outcomes of SARS-CoV-2, focusing on severity (hospitalization; mortality; ICU admission; the need for respiratory support) and risk of infection. Secondary aim was to assess the effect of vitamin D supplementation on these outcomes.

This review was designed to answer the following clinical research questions:

- Is vitamin D supplementation an effective and safe treatment option for SARS-CoV-2?
- Does vitamin D supplementation decrease the risk of SARS-CoV-2 infection?
- Does vitamin D supplementation decrease the risk of developing SARS-CoV-2 -related complications?
- Is vitamin D deficiency/inefficiency (25OHD < 20 or <30 ng/mL) or severe VDD (25OHD < 10) associated with a higher risk of severe SARS-CoV-2 infection (hospitalization; death; ICU admission; need for respiratory support) compared with vitamin D sufficiency (25 (OH) D < 20 vs. > 20 ng/mL) low–high levels?
- Do patients with SARS-CoV-2 infection have lower 25 (OH) D concentrations compared with those not infected with SARS-CoV-2?
- In meta-analyses with participants who were negative for SARS-CoV-2, did these individuals have higher 25 (OH) D concentrations than those who were positive for SARS-CoV-2?

- Does having a sufficient 25(OH) D status (>20 ng/mL) protect against SARS-CoV-2?

Clinicians, patients, managers, and policymakers might find the answers to the above important questions.

The body of this thesis consists of two main parts. The general part (part A) and the research part (part B) are separated into sections.

The first part, "General", describes the context of previously acquired knowledge. In order to indent what is already known about the 25 (OH) D and SARS-CoV-2 severity and risk of infection, a rapid evidence summary took place using PubMed, ClinicalTrials.gov of U.S national library of medicine and google scholar, without strict restriction. Part (A1) includes SARS-CoV-2 consequences and pathophysiology in the first section, vitamin D role in health and infections in the second section and the last section presents recent evidence and the reason to conduct this study, providing the research questions this thesis addresses.

According to the PRISMA checklist 2020, the research chapter (B) is split into three primary section. The first section (B1) presents the procedures that were carried out for this study and includes the following components: eligibility criteria, information sources, search strategy, selection process, data items, study risk of bias assessment, effect measures, synthesis methods, reporting bias assessment, certainty assessment, and finally, it summarizes and synthesizes the meta-analyses. Then the section (B2) presents the results of this review, including the following aspects: the meta-analyses selection, the meta-analyses characteristics, the results of individual meta-analyses, the results of quality syntheses of meta-analyses, reporting the biases of meta-analyses. The final section (B3) presents the discussion points and offers a comprehensive and critical evaluation based on the evidence that was gleaned from the reviewed meta-analyses.

A.1 SARS-CoV-2 infection and the consequences for Health

Coronavirus type 2 is responsible for the severe acute respiratory syndrome. The most common form of disease caused by Coronavirus is SARS-CoV-2. On the 11th of March 2020 the WHO preached the SARS-COV-2 infection as global pandemic (Bakhiet & Taurin, 2021)

The SARS-CoV-2 virus has had a significant impact on the lives of people all over the world (Lu et al., 2020).After the first cases were reported, the virus sequence was quickly analyzed and identified as an RNA virus belonging to the Coronaries family. The sequence revealed a close relationship between the virus and Bat's Betacoronavirus virus, which was initially reported in China. Variations in demographic distribution and the severity of disease can be found in various parts of the world (M. Pal et al., 2020). Patients with SARS-CoV-2 develop bilateral lung infiltration and hypoxemia which are responsible for the severe viral pneumonia brought on by immune overkill, excessive cytokines, and endothelial injuries (R. Chen et al., 2021) (Wu & Yang, 2020) The pathophysiology of SARS-CoV-2 , as well as the progression of acute respiratory distress syndrome (ARDS), is depicted in figure 1 (Belouzard et al., 2012), (Rohilla, 2021), (Banu et al., 2020). People who already have an underlying condition or who are over the age of 65 are at a greater risk of contracting SARS-CoV-2. The severity of the symptoms appears to range from mild to severe. Despite the implementation of stringent protective measures such as numerous restrictions on daily living, compulsory vaccination in some countries, and teleworking, unfortunately, it is still spreading uncontrollably. Different people experienced different symptoms when exposed to SARS-CoV-2. The effect that these limitations will have on the health behaviors and lifestyles that people engage at home is not yet known (Abduelkarem et al., 2022). According to the World Health Organization, (**https://covid19.who.int/**) as of the 6th of February 2022, the total number of confirmed cases SARS-CoV-2 around the world is approximately 394 million, with 5.74 million deaths, and approximately 317.8 million people have recovered from the illness. It is essential to make rapid progress in the research and development of effective therapeutic strategies for the treatment of infection as well as its prevention.

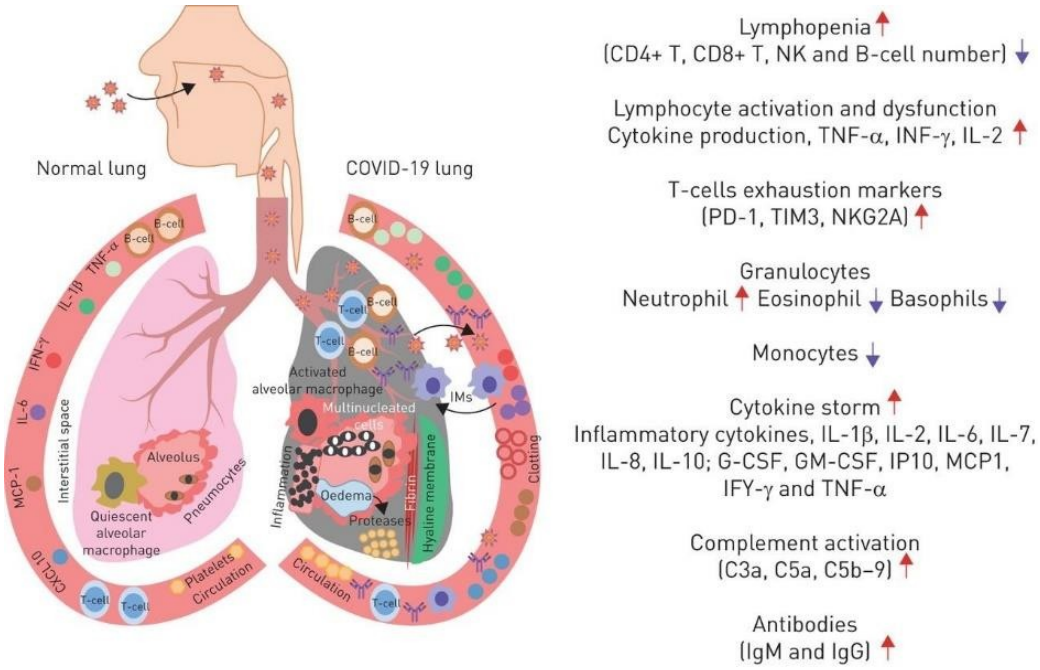
A.1.1 The Life Cycle of SARCS-CoV-2

The SARS-CoV-2 is extremely pathogenic and can cause infections ranging from mild to severe in the respiratory system. There is an explicit binding of the coronavirus spike (S) protein(s) to the cellular entry receptors during the first phase of the life cycle of SARS-CoV-2.These entry receptors include dipeptidyl peptidase 4 (DPP4; MERS- CoV), angiotensin-converting enzyme 2 (ACE2); SARS-CoV-2; SARS-CoV, HCoV-NL63, and human aminopeptidase N. (APN; HCoV-229E). The second phase involves tissue distribution in addition to the expression of entry receptors, both of which have significant influences on the pathogenicity and viral tropism of SARS-CoV-2. SARS-CoV-2 replicates its genomic RNA in addition to expressing it, which results in the production of full or complete-length copies. These copies will be incorporated or merged into newly formed or produced viral particles, as shown in figure 1. The RNA genomes of SARS-CoV-2 are unusually large and are flanked by 3' untranslated regions as well as 5' untranslated regions. These regions contain cis-acting secondary RNA structures that are necessary for the synthesis of RNA. The genomic RNA is distinguished by the presence of two open reading frames (ORFs; ORTF1a, b) that are significantly larger. These ORFs occupy approximately two-thirds of the polyadenylated and

capped genome. ORF1a and ORF1b are responsible for encoding the 15–16 non-structural proteins (nsp), of which 15 is responsible for composing the transcription complex (RTC) and viral replication, both of which involve RNA modification and RNA processing (V'kovski et al., 2021). As can be seen in Figure 1a, the SARS-CoV-2 virus contains structural proteins. These structural proteins include nucleocapsid (N), membrane (M), and envelope (E) proteins, in addition to the spike (S) protein. The presence of E and M guarantees that they will be incorporated into the viral particle. S trimers protrude from host-derived viral envelopes and provide specificities for cellular entry receptors. This is because S trimers are host-derived. The TNF-α plays a role in inflammation, immune system development, apoptosis and lipid metabolism. TNF-α is also implicated in a number of pathological conditions including asthma, Crohn's disease, rheumatoid arthritis, neuropathic pain, obesity, type 2 diabetes, septic shock, autoimmunity and cancer.

Concurrent with the expression of the individual non-structural proteins is the biogenesis of viral replication organelles. These organelles include small open double-membrane spherules (DMSs), convoluted membranes (CMs), and characteristic perinuclear double-membrane vesicles (DMVs). These organelles create a protective micro-environment for the transcription of sub-genomic mRNAs (sg-mRNAs), as well the structural proteins that have been translated are then translocated into the membranes of the endoplasmic reticulum (ER). These proteins then pass through the endoplasmic reticulum-to-Golgi intermediate compartment (ERGIC), where they interact with N-encapsidated, newly formed genomic RNA. This ultimately results in budding into the lumen of the secretory vesicular compartment (s). Exocytosis is the process that leads to the release of the SARS-CoV-2 virus from infected human cells (V'kovski et al.2021).

Figure 1: Lung pathophysiology, cytokine production as well as immune cell activation



Source: Adapted from (R. Kumar et al., 2020)

A.1.2 Finding Potential Treatments for SARS- CoV-2

As the virus continues to spread, new viral strains will inevitably emerge. Such as the delta (B.1 617.2) and omicron (B.1.1529) strains, which have the potential to cause a more severe illness or to spread the disease more quickly than the original virus. Knowing the extent to which new antibody treatments may be able to treat viral variants, thereby lowering the mortality rate and improving health outcomes, is an essential component of the search for new antibody treatments for SARS-CoV-2.

SARS-CoV-2, a virus that replicates in the cytoplasm, is encased by viruses that contain positive-stranded RNA. The nucleocapsid of the virus is effectively delivered into the host cells by the virus thanks to a process known as fusion, in which the virus' envelopes combine with the membrane of the host cell. As a result, a neutralizing monoclonal antibody, such as LY-CoV555, is able to have significant effects on the reduction of the SARS-CoV-2 viral load, which in turn results in a reduced rate of hospitalizations and improved health outcomes in SARS-CoV-2 patients (Jaworski, 2021). Specifically, administration of any one of three doses of the neutralizing antibody LY-CoV555 (700.0mg, 2800.0mg, or 7000.0mg) accelerates the natural reduction in viral load within 11 days, which results in fewer patients requiring hospitalization (Chen et al.2021). For instance, Chen et al. (2021) discovered that only 1.6% of SARS-CoV-2 patients who received one dose of the neutralizing antibody LY-CoV555 were hosp9italized or went to the emergency department, in comparison to 6.30% of those who were given a placebo. The dose of LY-CoV555 lessens the severity of the symptoms associated with SARS-CoV-2 . For instance, in comparison to SARS-CoV-2 patients who were given a placebo, patients who were given LY-CoV555 reported a significantly lower severity of SARS-CoV-2 symptoms between the second and sixth day after receiving a dose of 700 mg of LY-CoV555. This was the case between the second and sixth day after receiving a dose of 700 mg of LY-CoV555. Additionally, the neutralizing antibody LY-CoV555 reduces the amount of SARS-CoV-2 in the body. Those who received a dose of 2800.0 mg LY-CoV555, for instance, had a lower viral load when compared to the SARS-CoV-2 individuals who werein the placebo group (factor of 3.40). It was determined that there was a statistically significantdifference between the viral loads of the two groups (Chen et al., 2021). However, the ACTIV-3/TICO LY-CoV555 Study Group discovered that the combination of remdesivir and LY- CoV555 monoclonal antibody had no effect on SARS-COV-2 in patients who did not have end-organ failures (ACTIV-3/TICO LY-CoV555 Study Group, 2021).

The use of antiviral agents such as favipiravir, remdesivir, and umifenovir, among other potential treatment interventions, improves the health outcomes of SARS-CoV-2 patients.

In addition, hydroxychloroquine is utilized in the treatment of SARS-CoV-2. The results of a randomized clinical trial showed that dexamethasone lowers the risk of death in patients who have coronavirus; consequently, it can be used to treat patients with SARS-CoV-2 who are in a severe condition (Trivedi et al., 2020), (Bakhiet & Taurin, 2021) Hydroxychloroquine has been found to be ineffective in the treatment of SARS-CoV-2 in hospitalized patients, according to the findings of several randomized clinical trials. However these trials found that the drug causes severe adverse events. Patients with SARS-CoV-2 who were given hydroxychloroquine for a period of four weeks in a clinical trial that was randomized, controlled, and open-label in the United Kingdom found that the drug did not have a significant impact on reducing the mortality incidence (The RECOVERY Collaborative Group, 2021).

Similarly, (Hernandez-Cardenas et al., 2021) discovered that the administration of 400.0mg/day of hydroxychloroquine to SARS-CoV-2 patients for a period of 10 days did not have any significant beneficial or harmful effects on reducing the in-hospital mortality of people with serious respiratory diseases caused by SARS-CoV-2 .

In addition, the findings of a recent randomized clinical trial revealed that there is a significant difference between the incidence of death or major thromboembolism (28.70%) with therapeutic-dose heparins and 41.90% with intermediate/prophylactic-dose heparins. Thromboprophylaxis with therapeutic doses of lower-molecular-weight heparin plays an important role in reducing the outcomes of death as well as major thromboembolism and death in SARS-CoV-2 patients who are admitted with higher risks (Spyropoulos et al., 2021)

In a multicenter, double-blind, randomized, placebo-controlled trial, (Murai et al., 2021) investigated the impacts of a single high dose of vitamin D_3 on hospital length of stay in SARS-CoV-2 patients (n=240). Their goal was to determine whether or not high dose vitamin supplementation for severe SARS-CoV-2 infection is effective. The participants were given either a single oral dose of 200,000 IU of vitamin D3 (n = 120) or a placebo (n = 120) through a random assignment process. (log-rank p=0.59); not-adjusted hospital discharge's HR=1.070 (95.0% CI: 0.82.0-1.39.0; *p*=0.62) The findings showed that there was no significant difference in the length of stay between the placebo groups (7 (5-13) days) and the group that received vitamin D3 (7(4-10) days). Based on these findings, it appears that giving to SARS-CoV-2 inpatients a single high dose of vitamin D_3 does not significantly reduce the total amount of time they need to spend in the hospital. As a result, the findings of this study do not lend credence to the use of high doses of vitamin D_3 as a treatment for SARS-CoV-2 (Murai et al., 2021).

As a direct result of the worldwide vaccination campaign, more than 10.045.314.770 doses of the SARS-CoV-2 vaccine have been distributed all over the world. Additionally, therapeutic strategies play a significant role in the treatment of SARS-CoV-2 infections, the prevention of SARS-CoV-2 infection, and the suppression of the progression, which results in a lower mortality rate as well as less severe symptoms (Rohilla, 2021).

Both randomized and non-randomized clinical trials are currently being conducted in an effort to find new therapies that can be used immediately in clinical practice for the treatment of this pandemic, which has already claimed the lives of thousands of people. Interventional Studies (n=3.417) relative to SARS-CoV-2 are currently underway according the Clinical Trial gov (last seen, 07.02.2022).

Nutraceuticals include quercetin, lactoferrin, selenium, probiotics, cinnamaldehyde, curcumin, vitamin C, vitamin D, as well as Zinc. Additionally, the immune system is strengthened by these nutraceuticals, and they have significant anti-inflammatory, antioxidant, and antiviral effects, all of which are essential in the treatment of SARS-CoV-2 (Mrityunjaya et al., 2020).

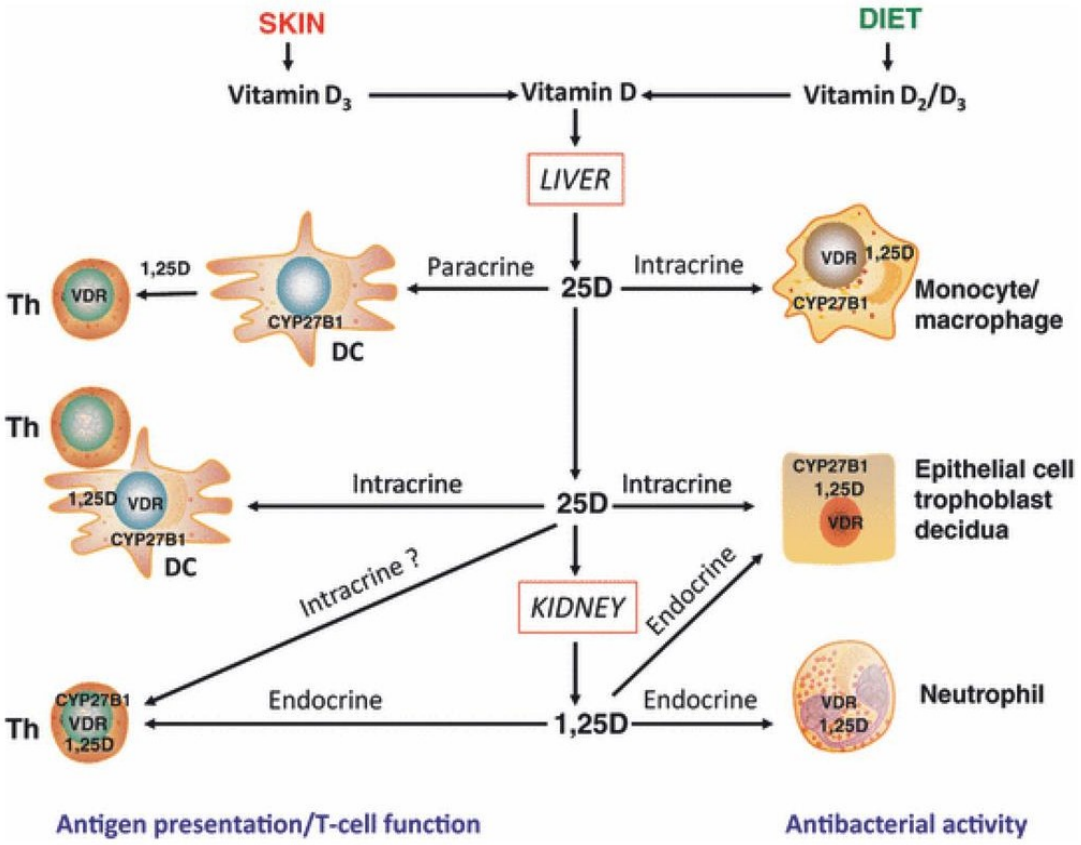
A.2 Vitamin D_3 Physiology and the Role in Health

Dietary sources and the body's own natural production of a precursor compound are the two ways that vitamin D_3 can be obtained. Vitamin D_3 is the predominant form of vitamin D found in the human body. The absorption of dietary vitamin D_3 occurs in the upper portion of the small intestine in a manner that is very similar to that of the absorption of other fat-soluble

compounds. After entering the circulation in the chylomicron fraction primarily via the thoracic duct, it then binds to a beta-globulin fraction in the bloodstream. This process takes place after the chylomicron fraction is in the blood. (Fiamenghi & Mello, 2021)

Vitamin D_3 lowers the risk of infections such as acute viral respiratory tract infections and pneumonia through a number of different mechanisms, including the direct inhibition of immunomodulatory ways or anti-inflammatory pathways, as well as viral replication. (Grant et al., 2020).

Figure 2: Mechanisms for adaptive as well as innate immune responses to vitamin D



Source: Adapted from (Prietl et al., 2013)

A.2.1 Does Vitamin D Decreases the Risks of SARS-CoV-2 Infection?

Through a mechanism involving defensins and cathelicidins, vitamin D lowers the risk of SARS-associated coronavirus type 2 infections. This mechanism lowers the concentration of pro-inflammatory cytokines while also slowing the rate of viral replication. On the other hand, not getting enough vitamin D, which is linked to having low 25 (OH) D concentrations, can increase chances of contracting SARS-CoV-2 infections and acute respiratory distress syndrome (Grant et al., 2020; Martineau et al., 2017). Therefore, people who are at risk of SARS-CoV-2 should consider taking supplement of vitamin D_3 which will improve the concentrations of 25-hydroxyvitamin D, in order to either prevent SARS-CoV-2 infections or reduce the risks of SARS-CoV-2 infections (Grant et al., 2020); (Kazemi et al., 2021). According to (Sahraian et al., 2020) vitamin D sufficiency in serum, at least 30 ng/mL can

reduce the risk of patients with SARS-CoV-2 infection experiencing negative clinical outcomes.

Modulating autophagy, antiviral proteins, and proinflammatory cytokines is how vitamin D lowers the risk of getting SARS-CoV-2 infection. To be more specific, vitamin D plays an important role in the process of triggering cellular events, which in turn modulates the immune system via the regulation of genes that are essential for the prevention and treatment of SARS-CoV-2 infections. In addition, vitamin D inhibits inflammatory processes and calms the cytokine storm that occurs in SARS-CoV-2.Additionally, vitamin D increases the production of antimicrobial and antiviral proteins in macrophages. These proteins, such as cathelicidin and human beta defensing-2, promote the removal of viruses from the cells via autophagy while inhibiting the replication of viral particles. This results in the prevention of SARS-CoV-2 infections and a reduction in the risks of SARS-COV-2 infection (Gilani et al., 2022).

Additionally, vitamin D supplements improve the expression of genes associated with autophagy, which controls apoptosis. Antimicrobial peptides suppress the production of proinflammatory cytokines and increase CD-11c+ cells, both of which help in preventing acute viral infections such as pneumonia and reducing the risks or mortality associated with SARS-COV-2 infections (Lei et al., 2017); (Werneke et al., 2021). Vitamin D supplements strengthen the immune system by stimulating the body's innate immune response, an aspect of immunity that is essential for warding off SARS-CoV-2 infections (P. Kumar et al., 2021); (Zemb et al., 2020). Vitamin D supplements raise vitamin D levels in the human body, which results in high production of glutathione (Brenner & Schöttker, 2020); (Kow et al., 2020); (Mitchell, 2020). Glutathione is essential in the treatment as well as the prevention of SARS-CoV-2 infections and mortality (Brenner & Schottker, 2020); (Kow et al., 2020). Vitamin D supplements can be taken at doses ranging from 100.0 to 250.0 micrograms per day for the amount of time that is recommended by a doctor or physician in order to raise the serum concentration of 25-hydroxycholecalciferol, which has numerous positive effects on one's health, including the prevention of SARS-CoV-2 infections (Charoenngam et al., 2020); (Feketea et al., 2021).

The immune responses of both the adaptive immune system and the innate immune system can be regulated by vitamin D, which is essential for the prevention of viral infections like SARS-CoV-2. The vitamin D receptors are responsible for the genomic effects of vitamin D. Genes that code for cathelicidin and vitamin D response elements, which are both involved in the fight against bacterial and viral infections, are regulated as a result of an interaction between vitamin D receptors and calcitriol. In the event of an infection, vitamin D signaling significantly modifies the epigenome in monocytes and models chromatin. This results in the modulation of innate immune responses and a reduced release of cytokines. Vitamin D, through its action on the epigenomes of immune cells, strengthens the innate immune systems, which in turn lowers the risk of contracting viral infections like SARS-CoV-2 while simultaneously increasing overall resistance to disease (Carlberg, 2019); (Gilani et al., 2022). Vitamin D is able to further regulate the functions or activities of T regulatory lymphocytes, which in turn suppresses inflammation that is out of control and protects against SARS-CoV-2 infections (Weir et al.2020). Enhancing the activity and role of T regulatory lymphocytes in attenuating antiviral defense against SARS-CoV-2 is one of the many benefits, that vitamin D provides to SARS-CoV-2 patients. Vitamin D also helps reduce inflammation-induced organ damage (Wang et al.2021).

Finally, vitamin D helps to prevent SARS-CoV-2 infection by upregulating the immune regulatory system and the expression of ACE2 while simultaneously downregulating the RAS pathway and the cytokine storm. This is an essential factor in the treatment of and prevention of SARS-CoV-2 infection (Gombart et al., 2020). The higher levels of anti-inflammatory and antifibrotic activities, as well as the release of angiotensin 1–7 in the body, are all significantly related to improved ACE2 expression. In most cases, vitamin D will increase the expression of the ACE2 gene, which will result in reduced inflammatory responses as well as reduced risks of SARS-CoV-2 infections and mortality (Tomaszewska et al., 2022).Vitamin D helps in the management of SARS-CoV-2 infections by enhancing the production and release of important antiviral molecules of the immune system called type I interferons. These interferons facilitate the rapid removal of the virus and suppress the replication of the virus. Vitamin D also helps in the management of other infections caused by SARS-CoV-2. The expression of the antithrombin gene is reduced by vitamin D, which makes the management of SARS-CoV-2 infections possible. (Bassatne et al., 2021); (Tomaszewska et al., 2022).

A.2.2 Association between SARS-CoV-2 and 25 (OH) D Deficiency, Inefficiency, Supplements

Recently, conflict studies reveal that VDD is associated with various diseases, such as depression, autoimmune diseases, cardiovascular disease, acute respiratory infections, as well as cancer (Sizar et al., 2022). VDD and insufficiency were defined as a 25 (OH) D level of <20 ng/mL (50 nmol/L) or as a 25 (OH) D of 21–29 ng/ml (52.5–72.5 nmol/L), respectively, and sufficient/normal if the 25 (OH) D level was ≥30 ng/ml.

Severe VDD results in various diseases and comorbidities. Nevertheless, further clinical trials should evaluate the effectiveness of diverse vitamin D supplements on SARS-CoV-2 infections for easy adoption of the vitamin D dosing plans for the specific population because the serum responses to the vitamin D dose provided vary between people as a result of biological, demographic and heterogeneity variables. Thus, taking these variables into consideration while providing vitamin D dosing plans for a population with VDD will not only reduce the risks of SARS-CoV-2 infections but prevent acute viral respiratory tract infections (Ali, 2020); (Azzam et al., 2022); (Fabbri et al., 2020); (Rawat et al., 2021).

Vitamin D inefficiency, deficiency and low levels of vitamin D supplements are related to infectious diseases, cardiovascular and autoimmune disorders. Increased risks of acute respiratory infections are related to vitamin D deficiency. In schizophrenia patients, VDD remains a modifiable risk factor for decreasing the severity of respiratory infections (Viani-Walsh et al., 2021).

The clinical trial found a causal association between severe SARS-CoV-2 and vitamin D deficiency, recommending that people with low vitamin D deficiencies should take Vitamin D supplements, which are clinically safe, to mitigate SARS-CoV-2 infections (De Smet et al., 2020);(Teshome et al., 2021) conducted a meta-analysis and systematic review on the effects of Vitamin D on SARS-CoV-2 infection based on 14 studies the meta-analysis and systematic review findings revealed a significant association between vitamin D_3 and SARS-CoV-2 infection. For example, high risks of SARS-CoV-2 infection were considerably associated with low serum VD (Teshome et al., 2021).

A.3 Evidence and Conflicts in Association between 25 (OH) D and SARS-CoV-2

Based on all the above references of previous studies underlined the important role of vitamin D in overall health as it has been confirmed that it helps to better function the immune system. The studies which support the role of vitamin D in reducing the risk of SARS-CoV-2 (Cutolo et al., 2020).

On the other hand, (Viani-Walsh et al., 2021b) did not found evidence that relates VDD and SARS-CoV-2 risks, severity and mortality. A recent meta-analysis of 2 RCTs and 11 cohort studies with 536,105 patients, findings revealed that Vitamin D supplementation didn't considerably reduce the ICU admission OR=0.140 and death OR= 0.570, I^2 = 64.0% in SARS-CoV-2 patients. Similarly, there was no significant decreases in the risks of SARS-CoV-2 related deaths OR=0.650; (95.0% CI: 0.40-1.06, I^2 = 79.0%) or SARS-CoV-2 infections OR= 0.920; (95.0% CI: 0.79-1.08, I^2 = 98.0%) and every 10.0 ng/ml rise/increase in serum vitamin D. Furthermore, there was no significant association between increase in in-hospital SARS-CoV-2 related death OR for < 20,00 ng/ml 2.180; (95.0% CI: 0.91-5.260, I^2= 72.0%); OR for < 30.0 ng/ml 3.07; (95.0% CI: 0.64-14.780, I^2 = 66.0%) or rise in SARS-CoV-2 infections OR for < 20.0ng/ml=1.61; (95.0% CI: 0.920-2.80, I^2 = 92.0%) and VDI < 30.0ng/ml or VDD < 20.0 ng/ml, p = 0.560. These findings imply that clinical outcomes in patients with SARS-CoV-2 were not significantly improved by vitamin D supplements. Also, vitamin D insufficiency or deficiency was not significantly associated with the vulnerability to SARS-COV-2 infections and related deaths. Generally, these findings suggest there was no significant relationship between clinical outcomes in hospitalized SARS-CoV-2 patients and vitamin D supplementation, as well as vitamin D levels and SARS-CoV-2 infections. For example, SARS-CoV-2 infections, risks of hospitalization and death were not significantly aggravated by low vitamin D levels (J. Chen et al., 2021).

Another recent systematic review and meta-analysis by Pal et al. (2022) that examined the relationship between clinical outcomes and vitamin D supplements in SARS-CoV-2 patients revealed that there was no association between enhanced clinical outcomes and vitamin D supplementation in SARS-CoV-2 patients. Also, there is no significant association between decreased mortality or ICU admission OR=0.41; (95.0% CI: 0.20, 0.810, p = 0.010, I^2 = 66.0%, random-effects model) and the use of vitamin D in SARS-CoV-2 patients. These findings imply that when administered after SARS-CoV-2 diagnosis, enhanced clinical and health outcomes were not associated with vitamin D supplementation (R. Pal et al., 2022)

Part B – Research Part

B. Materials and Methods

B.1.1 Guidelines followed

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (Prisma) 2020 (Appendix 1) The Cochrane handbook last version 6.2, (Higgins et al.,2021) was used to guide the systematic review. An a priori protocol developed following the guidelines was agreed on and signed by all members of the research team.

The systematic review questions, eligibility criteria, and search strategy were based on the Population, Intervention, Comparison, Outcomes and Type of study (PICOS) methodology (Table 1). Databases used in our search included PubMed, Embase, Scopus and Cochrane. Data extraction was completed in duplicate after independent screening for eligible studies according to defined criteria. Results were synthesized through structured tabulations and presented as a narrative description of qualitative evidence.

B.1.2 Eligibility Criteria

The meta-analyses that qualified for consideration in this study had to have the elements contained in the PICO questions (Table 1)

- Participants were positive or negative in studies that assessed the impact of the serum 25(OH)D levels on COVID-19 infection, vitamin D deficiency/insufficiency, supplementation or no supplementation, and a high vs. low 25(OH)D concentrations. Concerning study design, only meta-analyses were included.
- Vitamin D deficiency was defined as a serum 25(OH)D levels <50 nmol/L (20 ng/mL). Insufficiency was defined as 50–75 nmol/L (20–30 ng/mL). Normal values were considered 25(OH) D3 > 30 ng/mL (>75 nmol/L).(Holick et al., 2011).

Exclusion criteria

Systematic reviews without quantitative synthesis (meta-analysis), studies that were not related to the PICOS questions, studies with no structured methodology such as studies reporting unadjusted effect estimates or studies that did not report specific outcomes quantitatively, were excluded.

Table 1 : PICOS Framework for the Eligibility of Studies.

Population	Subjects participated in studies that assessed the impact of the serum vitamin D/supplementation level on SARS-CoV-2 infection
Intervention	I-1: VDD [25(OH)D < 20 ng/ml] or insufficiency [25(OH)D < 30 ng/ml] I-2: Vitamin D supplementation
Comparison	C-1: Supplementation vs. no upplementation C-2: Normal/high levels vs deficiency or insufficiency
Outcomes	O-1: SARS-CoV-2 severity (hospitalization; mortality; ICU admission; the need for respiratory support) O-2: SARS-CoV-2 risk (positive or negative, patients' condition)
Study	Meta-analysis

PICOS: population, intervention,outocomes,study; VDD: Vitamin D deficiency; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2 (2019).

B.1.3 Information Sources

At this stage, the reviewing team (PA, MPM) discussed the keywords constituting the search strategy and the criteria for including or excluding of the studies according to the PICOS strategy. A search of the electronic information systems, PubMed, EMBASE, Scopus and Cochrane library, used standardized and unstandardized keywords from 01.01.2019 up to 12.02.2022. The purpose of visiting the four databases is to ensure that the systematic search was comprehensive. Furthermore, targeted Google searches to provide additional sources, Cochrane SARS-CoV-2 study register, PubMed, SARS-CoV-2 information and clinical gov. did not result to more eligible studies. Language or publication status limits were not applied.

14 records did not have their full text, available for retrieval. Using the Taylor & Francis platform Open access https://www.tandfonline.com/ and because of library access of two universities and one hospital (National and Kapodistrian University of Athens, University of Lausanne and University Hospital of Lausanne) the full text retrieval was carried out successfully. The contact with two authors for key information and request for full texts for one edited research article, Kazemi, (2021) took place as well. All full texts of eligible articles were retrieved.

B.1.4 Search Strategy

The process of reviewing consisted of two stages of screening: (1) an examination of the title and abstract, and (2) an examination of the full text. Following the completion of the search, the titles and abstracts of the meta-analyses were screened in preparation for the selection process. An initial bibliographic review using the following algorithms (Table 2) was performed in order to find the studies that were being looked for. During this screening, was made sure that the title was relevant to the research question by checking it against a list. It was

possible to determine whether or not the meta-analyses had relevant results by screening the abstract. The second step was to conduct an analysis of the entire article using the inclusion criteria. Principal areas of emphasis included the vitamin D exposure that was the subject of the meta-analysis, as well as quality assessments, results, and conclusions.

Table 2: Detailed search strategies and MeSH. The literature search was conducted on 12 February 2022 on PubMed, Cochrane, EMBASE and Scopus.

Database	Search Strategy	Hits	Selection Studies	Duplicate's between Databases	Final Selected Articles
PubMed NCBI	meta-analysis AND (SARS-COV-2 OR SARS-CoV-2 OR 2019-ncov OR coronavirus OR (corona AND virus) OR coronaviridae) AND ('vitamin D' OR 'vitamin D3' OR calcitriol OR cholecalciferol OR colecalciferol)	58	32	Was the first database	28
Embase	'meta-analysis SARS-COV-2 vitamin d' OR (('meta-analysis'/exp OR 'meta-analysis') AND ('COVID 19'/exp OR 'COVID 19') AND ('vitamin'/exp OR vitamin) AND d)	90	28	27 comparatives with PubMed	1
Scopus	(TITLE-ABS-KEY ("vitamin D" OR "calcitriol" OR "cholecalciferol" OR "ergocalciferol" OR "alphacalcidol" OR "calcifediol" OR "1,25-dihydroxyvitamin D" OR "1,25-dihydroxy-vitamin D" OR "1,25-dihydroxyvitamin D3" OR "1,25-dihydroxy-vitamin D3" OR "1,25(OH)2D" OR "1,25(OH)2D3" OR "1α, 25(OH)2D" OR "1α, 25-dihydroxyvitamin D" OR "1α, 25(OH)2D3" OR "1α, 25-dihydroxyvitamin D3" OR "1α,25(OH)2D" OR "1α,25-dihydroxyvitamin D" OR "1α,25(OH)2D3" OR "1α,25-dihydroxyvitamin D3" OR "25-hydroxy-vitamin D" OR "25-hydroxyvitamin D" OR "25-hydroxy vitamin D" OR "25(OH) vitamin D" OR "25(OH)vitamin D" OR "25-OH vitamin D" OR "25OHD" OR "25-OH-D" OR "25(OH)D" OR "25(OH)-D" OR "25-OHD" OR "25-hydroxy-vitamin D3" OR "25-hydroxyvitamin D3" OR "25-hydroxy vitamin D3" OR "25(OH) vitamin D3" OR "25(OH)vitamin D3" OR "25-OH vitamin D3" OR "25OHD3" OR "25-OH-D3" OR "25(OH)D3" OR "25(OH)-D3" OR "25-OHD3")) AND (TITLE-ABS-KEY (" SARS-COV-2 " OR "COVID 19" OR "SARS-Cov" OR "SARS-Cov" OR "SARS-Cov-2" OR "SARS-Cov-2" OR "coronavirus")) AND (TITLE-ABS-KEY ("meta-analysis" OR "metaanalysis" OR "meta-analysis"))	104	22	22 comparative with PubMed	0
Cochrane	"vitaminD3" in Title Abstract Keyword OR "25-OH vitamin D" in Title Abstract Keyword AND "SARS-coronavirus" " SARS-COV-2 " in Title Abstract Keyword AND "meta-analysis" in Title Abstract Keyword - (Word variations have been searched)	55	0	0	0
	TOTAL	307	82	49	29

Two reviewers (MPM, PA) independently screened the titles and abstracts to identify eligible meta-analyses according to the eligibility criteria. Disagreements between reviewers did not exist. The flowchart by PRISMA is presented in figure 3.

B.1.5 Selection Process

The meta-analyses selected had a clearly defined research question, a detailed description of how the meta-analysis was performed, including the type of research designs, unit of measurement and subgroups limits of vitamin D were also taken into account, interventions and participant characteristics, findings, and discussion of findings.

The meta-analyses selected during the step abstracts and titles, were carefully examined in order to identify potential supplemental search terms (snow-balling technique). Then the meta-analyses that were selected for full-text review were examined carefully the risk of bias,

publication bias, and heterogeneity and type of included studies of each meta-analysis, were the main criteria for the quality appraisal. Case reports, case series, duplicate reports, commentaries, and author responses were excluded. All meta-analyses were then assessed for their quality before any retrieval of information. Two reviewers (MPM and PA) independently screened titles and abstracts and reviewed the full text of potentially relevant meta-analyses. They discussed questionable studies to agree on their possible inclusion in the present analysis.

B.1.6 Data Collection Process

The data were collected from the eligible meta-analyses screening independently two reviewers (MPM, PA) using a standardized data extraction form in excel manually. Manually also searched the references of included articles for the latest reviews.

A database platform for the data management was decided it would not be useful given the number of meta-analyses, thus a list of all the eligible meta-analyses was created carefully and with systematically screening every 2 days by the main reviewer (MPM) (Appendix 2). Database search results were combined and duplicate studies were removed manually. In case of overlapping meta-analyses, only the most recent one was included. Other relevant methods to process were described in the section information source.

B.1.7 Data Items

The exposure variables were the following:

1) The vitamin D supplements are either present or absent

2) The vitamin D levels deficiency < 20 ng/ml or insufficiency < 30 ng/ml in the serum of participants.

The outcome variables are healthcare outcomes, hospital admission, and length of hospital stays, need for respiratory support, mortality, ICU admission and the negative vs positive participants in the SARS-CoV-2 infection.

B.1.8 Study Risk of Bias Assessment

Systematic reviews and meta-analyses are highly susceptible to the risk of bias between or within studies, which can affect the validity and generalizability of conclusions. Almost all of meta-analyses had supplements tables that mentions the reporting bias of individual studies. In all meta-analyses, the search screening and the evaluation of eligibility studies performed by at least two reviewers independently. The methods and tools were used the included meta-analyses assess the risk of bias by the eligible meta-analyses are listed here.

The risk of bias between studies identified from Egger's and Begg's test (Higgins et al., 2019). Thus, in this systematic review the quantifying Publication Bias in included Meta-Analyses was determined by interpreting funnel plots, exporting the p-value of Begg's tests rank correlation, (Begg & Mazumdar. 1994) and Egger's regression test (Egger et al.1997) with a two-tailed. A p-value of less than 0.05 was considered as statistically significant.

Regarding to the risk of bias within in studies. The meta-analyses conducted the appraisal by two or three reviewers in individual studies using the Newcastle–Ottawa Scale (NOS). The

NOS is a scale to assess the quality of observational studies, case-control studies and cohort studies. The NOS scall was developed by the University of Newcastle in Australia and the University of Ottawa in Canada (Margulis et al., 2014).The range scale score fluctuates between one to nine. Any score ≥ 7 qualifies as high quality with a low risk of bias, while a score < 4 is categorized as low quality with a high risk of inherent bias. Any score in between is rated as moderate quality. Another quality assessment tool regarding to the observational studies of interventions or exposures is the Research Triangle Institute Item Bank (RTI–IB) scale of the USA agency for Health Care Research and Quality. Evaluates the conduct of observational studies included in systematic reviews, with a focus on bias and precision the scale include 29 multiple-choices items and the reviewers choices green color or a "+" whenan answer with low risk of bias, red or "–" reflect high risk of bias, and yellow or "?" when reflect an unclear risk of bias.(Viswanathan et al., 2008). Compare the two tools, the NOS scale required less tailoring and was easier to use than the RTI-IB, but the RTI-IB includes most of the domains measured in the NOS (Margulis et al., 2014).

The Cochrane Risk of Bias Tool 2 (RoB) use to assess the risk of bias in randomized trial clinical studies, is an update to the original risk of bias tool that launched in 2008. It has seven aspects to assess: Random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; and the selective reporting. The responses of options are: Yes; Probably yes; Probably no; No; No information. These responses distinguishing at the three levels: Low risk of bias; Some concerns; or High risk of bias. The relevant chapter in the Cochrane Handbook for Systematic Reviews of Interventions Chapter 8, titled '**Assessing risk of bias in a randomized trial**' Up-to-date information from the developers on RoB 2 is available via the Risk of Bias tools by Cochrane (Cochrane, 2020).

The ROBINS-I tool is recommended for assessing the risk of bias in non-randomized studies of interventions included in Cochrane Reviews. The score range to Low risk of bias when the study is comparable to a well-performed randomized trial with regard to this bias domain, Moderate risk of bias when the study is a non-randomized study with regard to this bias domain but cannot be considered comparable to a well-performed randomized trial. Serious risk of bias when the study has some important problems in this domain of bias and Critical risk of bias when the study is too problematic to provide any useful evidence. In addition, there is the level of "No Information".

Another tool is the Jadad scoring or the Oxford quality scoring system 'for evaluation the methodological quality of the clinical trials based on randomization, blinding, and withdrawals. They consists of five questions and the higher score indicates better RCTs quality. The scale range between 0 to 5. A study with a total score of < 3 is considered low risk of bias. (Berger & Alperson, 2009).

Some meta-analyses used the kappa statistic to assess the level of agreement during the risk of bias assessment by the two authors.

Furthermore, some meta-analyses used the of individual quality GRADE-PRO approach. Parameters of the Grade assessment give an overall rating for the quality of included studies. The GRADE-PRO focus on heterogeneity, inconsistency, publication bias, risk of bias, imprecision, and indirectness. The need to assess these variables was articulated by the aim of

ensuring that the studies are accurate and reliable. The scale of Grade Definition are (*High)* very confident that the true effect lies close to that of the estimation of the effect (*Moderate)* moderately confident in the effect estimate, *(Low)* confidence in the effect estimate is limited, and (*Very Low)* very little confidence in the effect estimate (Balshem et al., 2011)

B.1.9 Effect Measures

The effects measures were extracted from each meta-analysis, for binary outcomes (mortality, hospital admission, ICU admission) extracted the reported odds ratio (OR) or hazard ratio (HR) or Risk ratio (RR) and the corresponding 95% CI, for continues outcomes (length of hospital stay, serum levels) extracted the mean difference or a standardized mean different (SMD) or other relevant data (Tables 3-5). P-values of less than 0.05 were considered statistically significant. Heterogeneity of effect size estimates, it was defined by Q statistic and I^2. If Q is a lot larger than what expect under the null, conclude it's likely the studies in the meta-analysis are not estimating the exact same effect size. Regarding to the I^2 empirically a value below 50% indicates low heterogeneity, while a value up of 50 % indicates substantial heterogeneity.

B.1.10 Synthesis Methods

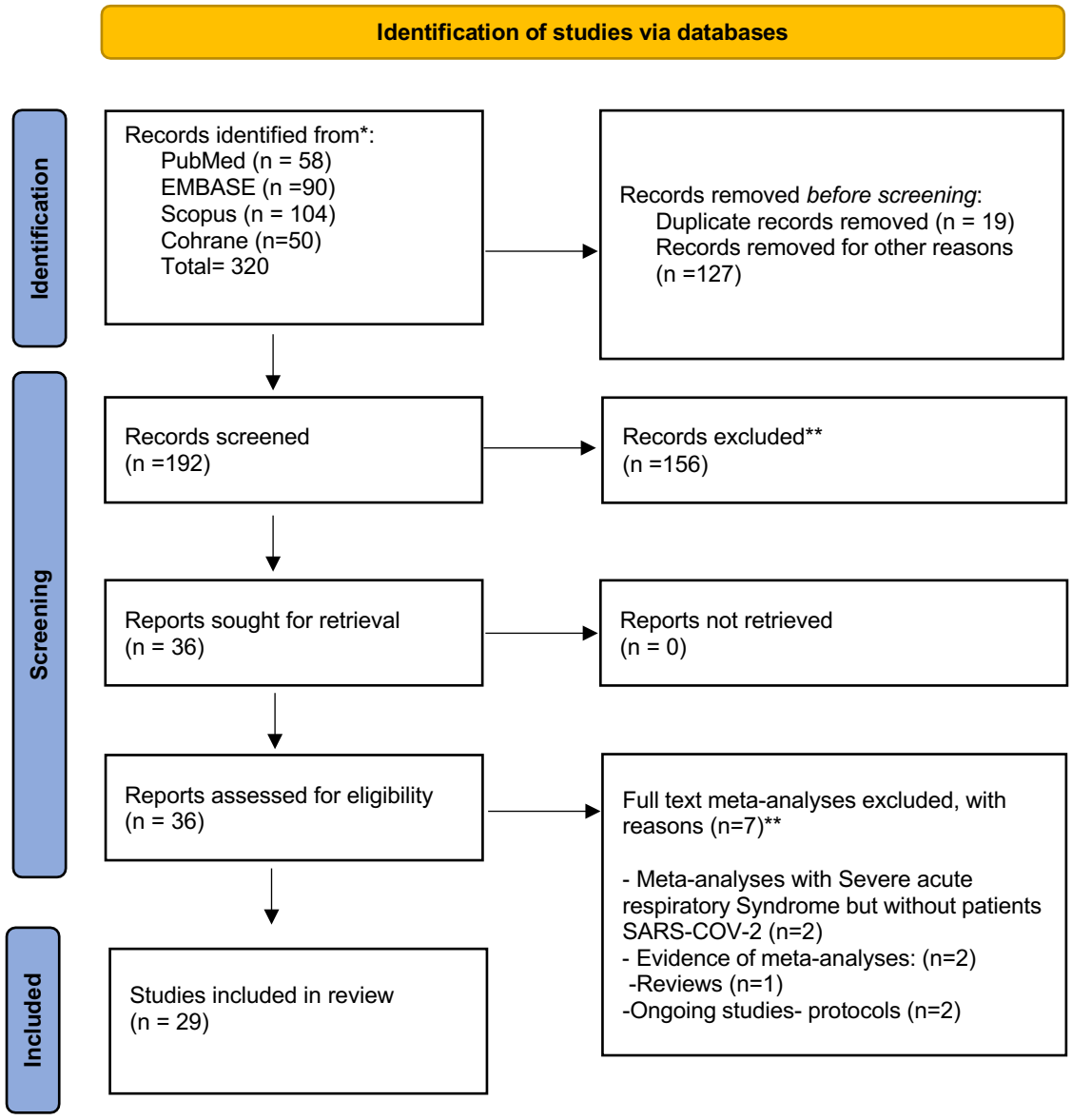
A separate qualitative synthesis was performed regarding meta-analyses on serum vitamin D levels and on vitamin D supplementation. Secondly, for each case, the meta-analyses were separately tabulated based on examining SARS-CoV-2 risk, severity or both (Tables.3-5).

B.2 Results

B.2.1 Study Selection

The initial search provided 320 articles, upon removal of duplicates, screening of titles and abstracts. After the initial screening, 90 duplicates were removed and 127 articles were further removed for other reasons such as other studies design or systematic reviews without quantitative synthesis or were irrelevant to research questions, after screening the abstracts and the titles of 102 articles. Then 158 studies were excluded, because they had an incomplete description of the methodology used in data collected or were just reviewed with results of meta-analysis, or it was letters to editors, or was corrigendum, or answers to editor or protocols. Thus, 36 studies were retrieved but the last control ruled out 7 studies, the reasons for exclusion are presented in Appedix 2b. Thus, 29 studies published up until the 12 February 2022 were retrieved and reviewed in the qualitative analysis. Study flow in a PRISMA flowchart (figure 3) (Munshi et al., 2021), (Ben-Eltriki et al., 2021), (Al Kiyumi et al., 2021), (Wang et al., 2022),(Halim et al., 2022), (Oscanoa et al., 2021), (Ebrahimzadeh et al., 2021) (Teshome et al., 2021), (Liu et al. ,2021), (Szarpak et al., 2021), (Ghasemian et al., 2021), (Pereira et al., 2020), (Kazemi et al.,2021), (Chiodini et al., 2021), (Kaya et al., 2021), (Akbar et al., 2021), (Varikasuvu et al., 2022),(Crafa et al., 2021), (Szarpak et al., 2021), (Beran et al., 2022), (Tentolouris et al., 2022), (Rawat et al., 2021), (Nikniaz et al., 2021), (Shah et al., 2021), (Hariyanto et al., 2022), (R. Pal et al., 2022), (Bassatne et al., 2021), (Petrelli et al., 2021), (J. Chen et al., 2021) (Appendix 2a).

Figure 3: Identification of studies via database



Titles of excluded studies:** *Risk of respiratory infections Effect of micronutrient supplements on influenza and other respiratory tract infections among adults: a systematic review and meta-analysis; Nutrient supplementation for prevention of viral respiratory tract infections in healthy subjects: A systematic review and meta-analysis; The Role of Vitamin D in The Age of SARS-COV-2 : A Systematic Review and Meta-Analysis Along with an Ecological Approach SARS-COV-2 Mortality Risk Correlates Inversely with Vitamin D3 Status, and a Mortality Rate Close to Zero Could Theoretically Be Achieved at 50 ng/mL 25(OH)D3: Results of a Systematic Review and Meta-Analysis; Optimum Solar Radiation Exposure or Supplemented Vitamin DIntake Reduce the Severity of SARS-COV-2 Symptoms Vitamin C and D supplementation and the severity of SARS-COV-2 : A protocol for systematic review and meta-analysis; Oral high dose vitamin D for the treatment of diabetic patients with SARS- COV-2 : A protocol for systematic review and meta-analysis*

B.2.2 Study Characteristics

The sample size of the studies ranged from 259 Nikniaz et al. (2021) to 1.407.715 Chiodini et al. (2021). The studies were conducted in Europe, (UK, Greece, Spain, Italy, Germany, France, Switzerland, Cyprus) USA (Mexico Australia) South America (Brazil) New Zealand, China, south Japan, Korea, Asia (Middle Eastern countries Israel, Iran, Indonesia, Saudi Arabia, Kuwait India), South Asia (Afghanistan, Pakistan maritime southeast Asia Singapore, East Asia (Mongolia) North Africa (Algeria) and Russia. All participants were above 18 years old.

Moreover, included studies of meta-analyses were observational, prospective and retrospective studies, randomized controlled trial (RCTs), cross-sectional studies (Data extraction tables. 3-5).

Subjects participated in studies that assessed the impact of vitamin D levels on SARS-CoV-2. The main outcomes of most studies were SARS-CoV-2 positivity severity and fewer SARS-CoV-2 risk of infection. The Severity scale for individual studies was mortality, hospital admission, length of hospital stays and intensive care unit admission.

B.2.3 Results of Syntheses, Reporting Biases of Meta-Analyses

B.2.3.1 Risk of Bias between Studies

The publication Bias was exported from individual meta-analyses base on Begg's and/or Egger's tests. Funnel plots in addition were carefully examined. The statistical assessment was two tailed and statistically significant p-value less 0.005.

In their meta-analysis by **Munshi et al. (2020)** a Funnel plot symmetry is listed. No evidence for publication bias for VDD and good vs poor prognosis, (*pE* =0.22) according to the pooled pairwise analysis of vitamin D levels in SARS-CoV-2 patients. However, the studies were five, to wit <10, thus indicating low reliability. **Ben-Eltriki et al. (2021)** did not provided information for the publication bias. In the meta-analysis of **Al Kiyumi et al. (2021)** Egger's regression intercept analysis was carried out for severity of symptoms and case fatality rate. It revealed a non-significant risk of publication bias for the association between low vitamin D levels and severity of symptoms (*pE*=0.071). However, the risk of publication bias was significant for the association between low vitamin D levels and mortality rate (*pE* =0.023). Illustrates the funnel plots and Egger's regression intercept. In meta-analysis **Wang et al. (2021)** according to the authors a publication bias for mortality was not find.(no data provided for funnel plot or Eggers). Begg`s test, in this meta-analysis was unable to statistically evaluate the other outcomes because < 10 studies. The following meta-analyses failed to provide information regarding publication bias. **Halim et al. (2021), Oscanoa et al. (2021), and Ebrahimzadeh et al. (2021)**. In their meta-analyses **Teshome et al. (2021)** there no indication for significant publication bias (*pE* = 0.764) for the main outcome risk of infection SARS-COV-2. In the meta-analysis of **Liu et al. (2021)** publication bias was explored by using funnel plots and Egger regression tests and revealed significant publication bias. Egger's test for both outcome, VDD/insufficiency was associated with an increased risk of SARS-COV-2 and SARS-COV-2 positive individuals had lower vitamin D levels than SARS-COV-2 - negative individuals *(pE*= 0.001*; pE* = 0.009). **Szarpak et al. (2021)** regarding to the meta-analysis of risk infection and VDD they are not available information for publication bias assessments similar in the meta-analysis of supplements due the limited studies n= 7 (<10).

Ghasemian et al. (2021) Begg's and Egger's tests did not reveal a publication bias of *(pB* = 1.00; *pE* =0 .55) for VDD and SARS-CoV-2 infection and a bias of (*pB* = 0.12; *pE* =0 .14) for VDD and SARS-CoV-2 severity. The bias for VDD and SARS-COV-2 mortality is *(pB* = 0.54; *pE* = 0.62). **Pereira et al. (2020)** The funnel plot of ten studies regarding the association between VDD and occurrence of several SARS-COV-2 show a satisfactory distribution within the funnel plot, indicated that there was no publication bias. However, publication bias was not assessed for the remaining outcomes because it was not appropriate for the assessment of prevalence in meta-analyses. In the meta-analysis by **Kazemi et al. (2021)** Egger's test, publication bias was evident in comparison of SARS-CoV-2–positive with–negative subjects (*pE* = 0.002). No publication bias in the comparison of severe and less-severe SARS-COV-2 patients (*pE* = 0.60); however, a small deviation towards an WMD −5 and an SE =2 was observed in a funnel plot. The meta-analysis by **Chiodini et al (2021)** has no indication of publication bias. The Egger's test estimation was used to evaluate the publication bias presence for ICU *pE*=0.816 <25 nmol/L *pE*=0.066<50 nmol/L, Insufficiency <75 *pE*=0.011, and Death *pE*=0,110<25 nmol/L *pE*=0.039<50 nmol/L *pE*=0.627 Insufficiency <75.

In the meta-analysis of **Kaya et al. (2021)** The Egger's test detected a publication bias in one of three outcomes, conducted in this meta-analysis. Thus there was no publication bias between the studies for infection and VDD *(pE*=0.399) and Mortality and VDD *(pE*=0,528) however a marginal significance indicated for Severity and VDD, (*pE*=0,054). Symmetrical Funnel plots are provided for all of three outcomes. The trim-and-fill adjustment method was performed. The meta-analysis of **Akbar et al. (2021)** showed that the qualitative funnel plot analysis was asymmetrical for mortality, severity, and susceptibility. Egger's test was indicated significant small-study effects for severity (*pE* = 0.047*)* and mortality *(pE* = 0.046*)*. There was no indication for publication bias (*pE*=0.615) similarly in the meta-analysis of **Varikasuvu et al. (2022)** was absent of publication bias. The funnel plot assessment with Begg's (*pB*= 0.17) and Egger's tests (*pE* = 0.14) on all the outcomes across all RCTs. p>1.

In the meta-analyses by **Crafa et al. (2021)** a low-risk bias was observed in the aspect of a high percentage of the 30 articles. The meta-analysis by **Beran et al. (2022),** suggested that high publication bias for studies that examined the effect of vitamin D supplementation & SARS-CoV-2 mortality. Egger's regression value of (*pE*=0.047) also is statistically significant. In the meta-analyses by **Tentolouris et al. (2021)** the Egger's and Begg's tests showed indication of absence any significant publication bias (p > 0.05) vitamin D supplementation SARS-CoV-2 mortality (*pE* = 0.68, *pB* = 0.41). However, the Egger's and Begg's tests showed that there was significant publication bias (p < 0.05) for ICU admission and vitamin D supplementation *(pE*=0.011, *pB*= −0.86) whereas visual inspection of bias was undertaken using Funnel plot. The meta-analyses bv **Rawat et al. (2021) and Nikniaz et al. (2021)** they are not available information for publication bias. **Shah et al. (2021)** Egger's and Begg's tests indicated the absence of any significant publication bias (P > 0.05) for ICU *(pB* = 0.11, *pE* = 0.25); mortality *(pB* = 0.11, *pE*= 0.13). The funnel plot illustrated a satisfactory distribution of the studies. It should be taken into account that the numbers of studies, (n=3) because normally publication bias was not assessed in the limited studies (n < 10). **Hariyanto et al. (2021)** Funnel plot analysis showed indication of publication bias was asymmetrical for the ICU admission and the need for mechanical ventilation. However, funnel plot analysis for the mortality showed a relatively symmetrical plot. There was no evidence of publication bias for ICU admission *(pB*=0.086), the need for mechanical ventilation *(pB*=0.060) or mortality outcome *(pB*=0.371).

Begg's test was not statistically significant. Because there were fewer than 10 studies in the ICU admission and mechanical ventilation outcomes, funnel plots and statistical tests for detecting publication bias are not as reliable as larger numbers of included studies in each outcome. **Bassant et al. (2021)** did not apply any subgroup analysis or publication bias assessment, because of the limited number of available studies for every outcome. **Petrellis et al. (2021)** the funnel plot indicates minimal publication bias in the primary endpoint analysis (*pE=0.04)* the quality of the evidence based on the GRADE approach is Characterized as "*very low*" for both outcomes of interest. Finally, in the meta-analysis of **Chen et al. (2021**) the publication bias was not assessed because of the limited studies (n < 10).

B.2.3.2 Risk of Bias within Studies

The majority of meta-analyses used the Newcastle–Ottawa Scale (NOS) for assessed the risk of bias within in studies. According the NOS scores as mentioned above, below 3 classified as very high bias, 4-6 moderate and 7-9 low bias.

There is no information available with quality assessment tool of the individual studies in the meta-analysis by **Munshi et al. (2020)**, however the six include studies were five retrospectives and one case-control studies reporting, serum vitamin D level and should be avoid claiming cause-effect relationships. **Ben-Elkrik et al. (2021)** does not provide information for the quality of the individual studies. In the meta-analyses by **AI Kiyumi et al.(2021)** Newcastle–Ottawa Scale (NOS) 36 out 43 studies had moderate risk of bias, whereas 2out of 43 low and 5 out of 43 high risk of bias. According the system score in this meta-analysis,the range was 0-9 for case–control and cohort studies, and 0-10 for cross-sectional studies. **Wang et al. (2021)** used also the Newcastle–Ottawa Scale tool. The risk of bias was high for 4out 7 studies, whereas 2 out 7 was a low risk, and 1 was a moderate risk. **Halim et al. (2021)**assessed the quality using the NOS (The Newcastle–Ottawa Scale). The NOS criteria in the cross-sectional studies were adapted from the cohort criteria 6 out of meta-analyses. A meta- analysis by **Oscanoa et al. (2021**) involved 23 studies, was used the NOS value of 8.1 indicating a low-risk bias. **Ebrahimzadeh et al. (2021)** 3 out of 13 studies had moderate bias 10 out of 13 had high according to the New Castle-Ottawa. **Teshome et al. (2021)** used the JBItool in order to evaluate the individuals studies, only studies with score of 50% included, the risk of bias characterized as moderate . In addition the kappa statistics used for agreements levels between two/or three reviewers. The meta-analysis by **Liu et al. (2021),** 8 out of 10 eligible studies were at low risk of bias, whereas 2 out of 10 were at moderate risk ofbias, according to the NOS scale. **Szarpak et al. (2021)** Rob tool present information for overscore 0–25% was low risk and 25-100% moderate risk. Moreover, the Robvis application wasused to visualize the risk of bias assessments. **Ghasemian et al. (2021)** In order to evaluate thequality for Observational Cohort, Cross-Sectional and Case-Control Studies, the Quality Assessment Tool was used. The analysis of all studies indicated that they were of fair quality.The Studies had a low risk of bias according to the Newcastle-Ottawa Scale (NOS). The results of quality assessment for studies entered into meta-analysis were fair. **Pereira et al. (2020)** a high risk of bias was observed in 20 out of 27 studies 25% was low and 75% high. In meta- analysis of **Kazemi et al. (2021)** the Newcastle-Ottawa scale (NOS) range between 3-6 indicated moderate risk of bias. **Chiodini et al. (2021)** according to the Newcastle-Ottawa scale(NOS) 35 studies had low risk, 6 high, 16 moderate. **Kaya et al. (2021)** used the Newcastle- Ottawa Scale (NOS) 17 studies had high risk and fair 5 low. In the meta-analysis by **Akbar et**

al. (2021) seven out of fourteen eligible studies were at low risk of bias, whereas 7 out of 14 were at moderate risk of bias, according to the NOS scale. **Variskasuvu et al. (2022**) used the Cochrane Risk of Bias tool (RoB 2) one out of six RCTs had high risk of bias one had low, whereas four RCTS had moderate risk of bias, because of "some concerns" related to randomization, blinding, outcome analysis and reporting of results. **Grafa et al. (2021).** All studies were judged to be of fair quality after analysis. **Szarpak et al. (2021)** (meta-analysis relative of supplements) using the RoB 2 tool and Robvis for randomized trials and the non-randomized trial studies,3 out of 6 were low, and 3 as moderate risk of bias. In the meta-analysis by **Beran et al. (2022),** the quality assessment of 13 studies examined the effects of vitamin D on mortality in SARS-COV-2 , 9 observational and 4 RTCs. Thus, four out of nine eligible studies were at low risk of bias, whereas five out of nine were at moderate risk of bias, according to the NOS scale, then all of four RCTs were low according <3 according to the Jadad composite scale. had high risk of bias, used the Cochrane risk-of-bias for randomizedtrials RoB 2 tool and ROBINS-I tool was used for the assessment the risk of bias of non- randomized trials. Presence of insignificant inconsistencies (minimum CI overlap and large variation in approximation effects) with no explanation. Furthermore GRADE characterized as"very low" for both outcomes. **Rawat et al. (2021)** Risk of bias graph showed 0-75%, indicating a low risk of bias and 25%, indicating an unclear result. The risk of bias summary was based on the Cochrane Systematic Review Guidelines The level of evidence, as qualifiedusing the GRADE was very low for all of three outcomes and the importance critical as well for all of three outcomes. **Nikniaz et al. (2021)** all studies had a low risk applied the Joanna Briggs Institute (JBI) Critical Appraisal Tools for (RCTs) and quasi- experimental studies. Most studies were of good quality. **Shah et al. (2021)** was used the Cochrane tool-quality of included studies were reasonably fair, as all three studies had a low risk of bias. Quality appraisal of studies included in the meta-analysis of **Hariyanto et al. (2021**) Jadad scale assessment 2 studies both have a good quality, all six studies were high quality according the Newcastle–Ottawa Scale cohort studies and case-controls, using Joanna Briggs Institute Critical Appraisal tool -case control studies all of 8 studies were high quality. In the meta- analysis of **Pal et al. (2021)** the Newcastle–Ottawa Scale (NOS) was used to assess the qualityof observational studies amd the Cochrane Collaboration instrument was used to assess the riskof bias for RCTs, the overall risk of bias was low. Then **Bassatne et al. (2021)** was used the NOS and Cochrane tool .Cross-sectional studies – high risk of bias for all studies and outcomes,one moderate, for Control studies 4 had low risk of bias and 3 high risk, For Cohort studies 19 studies evaluated as low risk, 20 high, and one moderate. All of three RTCs was unclear using the Cochrane risk of bias tool. **Petrelli et al. (2021)** 8 out of 43 eligible studies were at low risk of bias, whereas 35 out of 43 were at moderate risk of bias, according to the NOS scale. In the meta-analysis of **Chen et al. (2021)** the overall quality of the included studies was assessed by the Newcastle-Ottawa quality assessment scale (NOS), all of 9 studies had a low risk of bias scores <7. In additional was used the Cochrane risk of bias tool in order to assessed the RCTs studies (n=2), for both studies was clear in six out of seven different aspectsand one the aspect of ``other bias`` was unclear, for the both studies. Furthermore the GRADEcertainty characterized as" low", the GRADE importance table is presented for observational studies and for RCTs separately and was important for the outcomes of risk of SARS-CoV-19and mortality, ICU admission and critical for the mortality.

B.2.3.3 Heterogeneity

The Q and I^2 statistic test was performed from individual meta-analyses to assess in-between study heterogeneity (I^2 of < 25 %, 25–50%, 50–75%, and >75% indicating no, low, moderate, and high degree of heterogeneity, respectively).

In the meta-analysis of **Munshi et al. (2020)** significant heterogeneity was observed (I^2= 99.1%, p <0.0011) for Vitamin D serum level in positive patient. However, when applied the Radom effect models, the there is no indication of heterogeneity (I^2 =0.00% p<0.00) for prognosis poor vs prognosis good. **Ben-Eltriki et al. (2021)** significant heterogeneity for all of four outcomes association between vitamin D levels and SARS-CoV-2 severity (I^2=92%, p<0,00001), association between vitamin D levels and all-cause mortality (I^2 =68%, p<0,0001), association between vitamin D levels an d need for mechanical ventilation (I^2 =65%, p=0,001) and finally the heterogeneity of the studies were very high for three out of four biological markers and association with severity, association between vitamin D and D-dimer (mg/mL) levels (I^2=92%, p <0.00001), association between vitamin D and interleukin-6 (mg/mL) levels ((I^2=81%, p<0.0001), association between vitamin D and C-reactive protein (mg/mL) levels (I^2=100%, p<0.00001), however no heterogeneity for association between vitamin D and D-dimer (mg/mL) levels (I^2=0%, p=0,55).Random-effect model used. In the meta-analysis by **Al Kiyumi et al. (2021)** observed considerable heterogeneity for VDD and VDI severity *(I^2* = 67% p<0,00001), three studies were the cause for heterogeneity according to sensitive analyses. When these studies omitted heterogeneity may was not important (I^2 =23%, p=0.25) and the effect size was still significant. OR =2.51, (95% CI: 1,79-3,52, p<0,00001). Then, when they compared the levels of vitamin D low vs High with severity a significant heterogeneity was observed (I^2 =96%, p=0,000) in addition, considerable heterogeneity between studies for mortality (I^2=36*,* p=0,06 %) the heterogeneity was not important after the sensitive analysis (I^2 =0%, p=0.56). The random-effects model was used. The heterogeneity across the studies in meta-analysis by **Wang et al. (2021)** was not substantial for Mortality rate (I^2=30.5%, p=N/A, I^2=11,6%, p=N/A), Hospital admissions (I^2 = 0%, p=N/A) however was substantial for hospital stay (I^2 = 89.6%, p=N/A), and ICU *(I^2* =83,1%, p=N/A). In addition, conducted Subgroups based on cut-offs the geographic location, and the latitude gradient. In the meta-analysis of **Halim et al. (2022)** high heterogeneity was in all following outcomes: TNF-a & Severity (I^2=63%, p=<0,04) TNF-a & Mortality (I^2=80%, p=0,008), IL-6 &Severity, (I^2=86%, p<0,00001), IL-6 &Mortality *(I^2* =81%, p<0,000001), Severity & SARS-CoV-2 (I^2 =94%, p<0,000001), VDD mortality crude (I^2 =75% p=0,02) and VDD Mortality adj. (I^2 =66% p=0,02) in this reason radon effects models applied as results not substantial heterogeneity. **Oscanoa et al. (2021)** High risk of bias for both severity (I^2 = 83.3%, p=0.000) and mortality (I^2 =81.2%, p=0.000) **Ebrahimzadeh et al. (2021) high heterogeneity** Mortality (I^2 =71.1%, p=0.0080) fixed effect analysis was used for all subgroups. In their meta-analysis by **Teshome et al.2021** was observed significant heterogeneity between studies for the main outcome that's it the VDD and risk infection of SARS-CoV-2 (I^2 = 71.9% p=0.0002) in this instance the reviewers applied the random effect model and fixed-effect model. Subgroup analysis base on study design shown no heterogeneity between cohorts (I^2=0,00%, p=0,58), however the heterogeneity was high between cross sectionals studies *(I^2*= 75%, p=0,0002) and Case controls studies(I^2 = 85%, p<0,0001). According to the sensitivity analysis, two studies were the main reason for the heterogeneity. **Liu et al. (2021)** the heterogeneity was high for both outcomes first comparative low levels increased the risk (I^2=64.9%, p = 0.036) and positive individuals had lower vitamin d levels than negative individuals I^2 =89.6% **Szarpak et al. (2021)** (I^2= 99% p< 0.0001) **Ghasemian et al. (2021**) did not proved I^2 in their forest plot. **Pereira et al. (2020)** was high for VDD(<50 nmol/L) risk of infection. *(I^2* =78.5%, p=0,003). SARS-CoV-2 patients

had lower concentrations in the serum *(I^2* = 99.5%, *p*=N/A) and mortality (I^2= 59.0%, *p*=0,045) however the heterogeneity was low for the association between VDD and occurrence of several SARS-COV-2 (I^2= 35.7% *p*=0.122) and no heterogeneity for hospitalization, (I^2= 0.0%, *p*=0,872) **Kazemi et al. (2021)** evaluated using Cochrane's Q test, deriving its magnitudefrom the I^2 value. Risk of infection was moderate (I^2=44.2% *p*=0,167 crude), infection risk (I^2 =33.0% *p*=0, 20 Adjusted).No heterogeneity for Severity Effect size (I^2 = 0.0% *p*=0,001) adj., however was very high when was analysis as crude (I^2 =90.8% *p*=0,46), finally moderate heterogeneity observed for mortality when analyzed as adjusted (I^2=47.9% *p*=0,104), and high when analyzed as crude (I^2 = 84%, $p \leq 0{,}001$). In their meta-analysis **Chiodini et al. (2021**) analyzed four different outcomes primary was the SARS-COV-2 Severe ICU admission , secondly was the mortality third was SARS-CoV-2 infection susceptibility and the lastly was the SARS-COV-2 related Hospitalization which divided into three categories each for them VDD <25 nmol/L, VDD <50 nmol/L, VDI <75 nmol/. Thus, heterogeneity was high for SARS-COV-2 Severe ICU admission and VDD <25 nmol/L (I^2 =83%, *p*=0,094), as well highfor VDD <50 (I^2 =72%, *p*=0,09), however was moderate for VDI<75 for (I^2 =44%, p=0,06).Then for the second outcome which was mortality risk the heterogeneity was moderaterelated for VDD<25 nmol/L death and severe (I^2 =42%, p=0,33),high for VDD <50 (I^2 =70%,*p*=0.001) and as well high for VDD <75nmol/L *(I^2*=77, p=0.10). The third was the SARS- CoV-2 infection susceptibility and was high for all of three categories (I^2 =79%, p=0.10) severedeficiency <25 nmol/L, then (I^2 =88%, *p*=0.03) deficiency <50 nmol/L and (I^2 =78%, *p*=0,5) for insufficiency <75 nmol/L. Lastly regarding the SARS-CoV-2 related Hospitalization, the heterogeneity was marginally moderate to high (I^2=57% *p*=0,40) for severe deficiency <25 nmol/L same for deficiency <50 (I^2 =60%, *p*=0.25), however no indication for heterogeneity for insufficiency <75 nmol/L (I^2 =0%). In the meta-analysis of **Kaya et al. (2021)** heterogeneity was high for infection in the meta-analysis for serum 25 (OH) D levels <20 ng/mL or 50 nmol/L (I^2 = 85.4%,p <0,01); as well for Severity I^2 =92%, p<0,01) and mortality(I^2 = 83%, p<0,01).**Akbar et al. (2021),** high heterogeneity between SARS-CoV-2 risk and Infection (I^2= 92.6%, *p*=0,00) marginally moderate for Disease severity (I^2 =64,25%, *p*=0,02),and for Mortality rate (I^2= 80.27%, *p*=0,00). **Varikasuvu et al. (2022)** the overall heterogeneity was moderate (I^2 =48%, *p*=0.03). More specifically for each outcome was, moderate for severity (I^2 = 52%, *p*=0.06), low for mortality (I^2= 33%, *p*=0.21), no heterogeneityfor COVID RT-PCR positivity (I^2 = 0%, *p*=0.78), and did not showed for seropositivity because was only one study. **Grafa et al. (2020)** was high heterogeneity for all of three outcomes: a) for infection, (between level of vitamin D with the risk of infection SARS-CoV-2 in positive and negative patients as a continuous variable)(I^2=95%, *p*<0,0001) as well for severity (VD levels in patients with severe or non-severe COVID-19) (I^2=98%, *p*<0,00001) and for mortality,(SARS-COV-2patients who died compared to those discharged) (I^2=86%, *p*<0,00001).Regarding for subgroups in the three different categories was high for VD<20ng/ml (I^2 =81%, *p*<0,00001), no heterogeneity for VD<12ng/ml, (I^2=0%, *p*=0,95%) and heterogeneity was not applicable for VD<10ng/ml because of only study. **Szarpak et al. (2021)** no heterogeneity for ICU Admission *(I^2* =0% *p*=0.48) moderate for severity (I^2 = 48% *p* = 0.01) and was high for mortality (I^2 = 74%, *p*=0,002). Heterogeneity in the meta-analysis of **Beran et al. (2022)** was high for mortality and supplements *(I^2*= 77%, *p*<0,00001) and moderates for (I^2= 48%, *p*=0,10) for intubation rate, however no indication for heterogeneity for Length of hospital stay (I^2=0%, *p*=0,43). Subgroup analysis showed that vitamin Dsupplementation was not associated with a mortality benefit in patients receiving vitamin D pre(I^2=79%, *p*=0,001) or post SARS-CoV-2 diagnosis *(I^2* = 69%, *p*=0,001%). **Tentolouris et al. (2021)** significant heterogeneity for both outcomes (I^2 =62.4%, *p*=0,006) mortality, (I^2= 60.09%, *p*=0,028) supplementation and intensive care unit admission, were used Random- effects model. **Rawat et al. (2021)** moderate heterogeneity for Mortality (I^2 = 58%, *p*=0,07),

high for invasive ventilator (I^2 =91%, p=0,0007), also high for ICU admission (I^2 =89%,p=0,003) and did not refer the heterogeneity for N/A for changes in inflammatory markers. **Nikniaz et al. (2021)** Heterogeneity was not significant and was reduced by a sensitivity analysis. (Q = 1.514, df = 2, I^2 =0.000, p= 0.469) for studies between VDD and Mortality. **Shah et al. (2021)** Q statistics (significant at p < 0.10) and I^2 no heterogeneity as indicated (I^2 =21.71%, p= 0.27). **Hariyanto et al. (2021)** heterogeneity was high for Vitamin D and ICU admission *(I^2* = 70%, p=0,010), and moderate between vitamin D and need for mechanical ventilation (I^2= 61%, p=0,02) and for mortality (I^2= 50%.p=0,03). In the meta-analysis of **Pal et al. (2021)** was observed moderate heterogeneity (I^2 = 66%,p=0,001) for mortality and high for SARS-CoV-2 risk of admission *(I^2* = 80%,p=0,003). Regarding the subgroups adjusted of vitamin D supplementation on clinical outcomes ICU and mortality as compared to non-use of vitamin D when expressed as pooled odds ratio was high (I^2 = 74%, p=0,0007) and when expressed as pooled hazard ratio was very low *(I^2*=12%, p=0,29). **Bassatne et al. (2021)** significant heterogeneity observed for SARS-CoV-2 mortality (I^2=76%, p=0,0004) and ICU admission (I^2=85%, p=0,001), for disease severity (I^2 =77%, p=0,04) and for positivity status SARS-CoV-2 (I^2=76%, p=0,02).However was low for invasive requirement for mechanical ventilation/non-invasive requirement for ventilation, (I^2=0%, I^2=23%), for the hospitalization did not refer, however no heterogeneity for time of hospital stay (I^2=0%, p=1.00). **Petrelli et al. (2021)** high for severity *(I^2* =87%, p<0,0000), however not provided for risk infection. Finaly in the meta-analysis of **Chen et al. (2021)** the heterogeneity was high for all outcomes, between supplements and Mortality (I^2 =64%, p=0,009%),mortality as categorical (I^2 =79%,p=0,008) and as continuous I^2=66%, p=0,09),between supplements and admissions (I^2= 90%, p=0.001),between supplement and infection as categorical (I^2 = 98%, p<0.00001) and as continuous variable (I^2 =92%, p<0,000001).

Overall heterogeneity of individual meta-analyses appeared to range between high and moderate. The majority of meta-analyses they faced the heterogeneity, using the sensitivity analysis to clarify the heterogeneity between studies, performing subgroups analyses, and/or fix and random effect models for ensured the valid calculation of the effect size estimate.

B.2.4 Results of Individual Studies

This Systematic review found that a low serum 25 (OH) D level was significantly associated with disease severity (hospitalization; mortality; ICU admission; the need for respiratory support) and a higher risk of SARS-CoV-2 infection.

In the first group of SARS-CoV-2meta-analyses, the severity of serum deficiency/insufficiency was examined and a strong association was shown.

According to the meta-analysis **by Munshi et al. (2021)** patients with a poor prognosis (n = 150) had significantly lower serum levels of vitamin D than those with good prognoses (n = 161). The adjusted standardized MD=0.58, (95% CI: 0.83 to 0.34, p=0.001). The meta-analysis by **Ben-Eltriki et al. (2021)** conducted a pooled odds analysis, showing that VDD increases the risk of pneumonia RR=1.50; (95% CI:1.10–2.05), the risk of mortality RR= 1.60 (95% CI: 1.10–2.32), and the rate of hospitalization RR=1.14; (95% CI: 0.87–1.50). Furthermore, the meta-analysis found that patients with a VDD (troponin and D-dimer) had lower levels of cardiac biomarkers. VDD was associated with elevated levels of inflammation biomarkers CRP and IL-6. (95% CI: -0,26—057, p=0,09). **Al Kiyumi et al. (2021)** found a moderate association between VDD and SARS-CoV-2 symptoms OR=3.38; (95% CI: 1.94–5.87, $p < 0.0001$). In addition, VDD and insufficiency were associated with mortality OR=2.30; (95% CI: 1.47–

3.59, *p=0.0001*). The majority of the individual studies included in this meta-analysis were observational studies of moderate quality. The meta-analysis by **Wang et al. (2021)** found an increased risk of mortality due to low Vitamin D levels OR=2.47 (95% CI: 1.50–4.05); HR= 4.11, (95% CI: 2.40–7.04), and higher hospitalization rates OR=2.18, (95% CI: 1.48–3.21) and prolonged hospitalization (+0.52 days; 95% CI: 0.25–0.80). **Halim et al. (2022)** examined the relationships among TNF-α, IL-6, vitamin D, and SARS-CoV-2 severity and mortality. The pooled results show that the vitamin D levels of patients with severe SARS-COV-2 were not significantly lower than those of non-severe SARS-CoV-2 patients MD=−5.0232; (95% CI: −11.6832 - − 1.6368; $p = 0.14$). VDD insignificantly increased the risk of mortality in SARS-CoV-2 patients OR=1.3827; (95% CI: 0.7103−2.6916; $p = 0.34$). The IL-6 level was identified as an independent prognostic factor for the severity and mortality of SARS-CoV-2. **Oscanoa et al. (2021)** found vitamin 25 (OH) D deficiency to be associated with a higher rate of severe COVID-1 RR=2.00; (95% CI:1.47 − 2.71,) and a higher mortality rate RR=2.45;(95% CI:1.24 − 4.84,). The concentration of 25-hydroxyvitamin D was shown to influence the SARS-CoV-2 severity and the mortality rate. Subgroup analyses were conducted to assess the effects of age, sex, and the use of an alternative (25 (OH) D cut-off value <30 nmol/L) separately. A higher severity risk was found in people older than 60 years of age ($p = 0.040$).

Ebrahimzadeh et al. 2021 evaluated the relationship between categorized serum vitamin D and the risk of SARS-CoV-2 in-hospital mortality and the association between vitamin D as a continuous variable and the and risk of SARS-CoV-2 in-hospital mortality. Based on the pooling of nine studies reporting serum vitamin D levels, SARS-CoV-2 in-hospital mortality was significantly related to VDD OR=2.11; (95% CI:1.03-4.32). Subgroups analyses examined the age (≤60 years and >60 years, the duration of data collection (≤8 weeks and >8 weeks, studies geographical (middle-east countries and other countries), and studies sample sizes ≤180 participants and >180 participants, also showed an inverse significant relationship between serum vitamin D level and risk of in-hospital mortality from COVID-19.

The SARS-CoV-2 risk of infection and serum deficiency/insufficiency are strongly associated, according to three studies.

In the meta-analysis of **Teshome et al. (2021)** found that vitamin D-deficient individuals were at greater risk of SARS-CoV-2 infection than vitamin D-sufficient individuals. As compared with participants with sufficient vitamin D, VDD increased the SARS-CoV-2 risk by 80% OR=1.80; (95%CI: 1.72, 1.88). A low serum 25 (OH) Vitamin-D level was significantly associated with a higher risk of SARS-CoV-2 infection. Subgroup analysis applied base on study design and revealed an increasing trends with the case control studies and risk of SARS-CoV-2 infection. Similarly, **Liu et al. (2021)** investigated the Overall pooled OR in the fixed-effect model and showed that VDD or insufficiency was associated with an increased risk of SARS-COV-2 OR=1.43, (95% CI: 1.00–2.05). In addition, SARS-CoV-2 -positive individuals had lower vitamin D levels than SARS-CoV-2 negative individuals SMD=-0.37; (95% CI: −0.52 to −0.21). Lastly, the study of **Szarpak et al.2021** presented thirteen studies including data from 14,485 participants which showed that the vitamin D level in negative patients was 17.7 ± 6.9 ng/mL, while in positive patients, it was 14.1 ± 8.2 ng/mL MD=3.93; (95% CI 2.84–5.02; $I^2 = 99\%$; $p < 0.001$). Low serum vitamin D levels are statistically significantly associated with the risk SARS-CoV-2 infection. This suggests that supplementation of vitamin D is indicated, especially in groups at risk of deficiency.

In the third group, eight studies evaluated the associations of both the severity and risk of infection with the vitamin D serum level.

Ghasemian et al. (2021) found that VDD increased the chance of developing severe SARS-CoV-2 by 5 times OR= 5.1 (95% CI: 2.6–10.3) compared with having a sufficient vitamin D2 status. The odds of getting infected with SARS-CoV-2 were 3.3 times higher among individuals with a VDD (95% CI, 2.5–4.3), However, no significant association was found between vitamin D status and higher mortality rates OR= 1.6, (95% CI: 0.5–4.4). **Pereira et al. (2021)** did not found any association between VDD and a higher risk of SARS-CoV-2 infection OR ¼ 1.35; (95% CI¼ 0.80–1.88) $p = 0.003$. However, the values of serum vitamin D in patients with ARS CoV-2 were lowest WMD = −17.02 (95% CI:−29.61 −4.43). Additionally, the findings indicate that VDDcauses more severe cases of disease OR=1.64 (95%, CI:14.130-2.09). The rate of hospitalization was found to increase with vitamin D deficiency/inefficiency OR 14.18; (95% CI:14.141–2.21, $p = 0.8724$). Additionally, VDD increased mortality OR=14.2; (95% CI:1.06–2.58). **Kazemi et al. (2021)** showed a higher risk of infection in the patients with VDD OR:1,75; (95% CI:1,44-2,13) adjusted. The severity in the VDD group was higher OR=2,57; (95% CI:1,65- 4,01). Furthermore, there was a significant association of VDD with mortality OR= 2,62; (95% CI: 1,13-6,05) in crude and adjusted studies that used the Cox survival method HR=2.35; (95%CI: 1.22-4.52), indicating a significant association with VD. However, in adjusted studies that used a logistic regression, no relation was observed for mortality OR= 1.05; (95% CI: 0.63-1.75). **Chiodini et al. (2021)** found an association between ICU admission and severe deficiency OR=2.63; (95%CI:1.45–4.77), Deficiency OR=2.16; (95%CI: 1.43–3.26) and insufficient vitamin D, for ICU OR= 2.8; (95% CI:1.74–4.61). Mortality was associated with a severe VDD, VDD, and VDI OR=2.60; (95% CI: 1.93–3.49); OR:1.84; CI:1.26–2.69; OR: 4.15, 1.76–9.77, respectively). The Risk of Infection (OR, 95%CIs: 1.68, 1.32–2.13; 1.83, 1.43–2.33; 1.49, 1.16–1.91, respectively) and Hospitalization (OR, 95%CIs 2·51, 1·63–3·85; 2·38, 1·56–3·63; 1·82, 1·43–2·33, respectively) were also associated with severe vitamin D deficiency, deficiency, and insufficiency. VDD may increase the risk of infection with SARS-CoV-2 and the likelihood of severe disease, according to **Kaya et al. (2021).** Among patients with low levels of vitamin D, the risk of contracting SARS-CoV-2 was 1.64 times higher (95% CI:1.32 -2.04; $p = 0.001$).

An association was found between mortality and infection severity in the meta-analysis by **Akbar et al. (2021**). The rate of severity was 42% (22–62%). Mortality occurred in 24% (6–41%) of patients in the pooled analysis. The infection rate was increased in patients with low serum Vitamin D levels compared with the control group OR= 2.71 (1.72, 4.29), $p < 0.001$). Patients with low serum 25(OH) D levels had greater disease severity OR = 1.90; (95% CI:1.24, 2.93, $p = 0.003$) than the control group. The additional Mortality rate was also higher in individuals with Low serum 25 (OH) D OR=3.08, (95%, CI: 1.35-7.00, p=0.011) than in the control group. Furthermore, a Meta-regression analysis showed that the association between low serum 25 (OH) D and mortality was affected by male gender OR=1.22; (95% CI: 1.08-1.39, $p = 0.002$) and diabetes OR =0.88; (95% CI: 0.79 -0.98), p=0.019). **Varikasuvu et al. (2022)** Based on the overall collective evidence from all RCTs, vitamin D intervention is beneficial for SARS-CoV-2 patients RR=0.60, (95% CI: 0.40-0.92, $p = 0.02$). RT-CR positivity rates were significantly lower in the intervention group RR=0.46, (95%CI: 0.24-0.89, p= 0.02).

Patients who received vitamin D supplements demonstrated reduced rates of ICU admission, mortality events, and RT-PCR positivity according to **Grafa et al. (2021).** The meta-analysis included 30 articles. Those with a SARS-CoV-2 infection had significantly lower serum 25(OH) D levels than those without an infection MD= -3.99 (95% CI:−5.34, −2.64; $p <$ 0.00001) Additional serum levels were significantly lower in patients with severe disease MD= −6.88 95% CI:(−9.74, −4.03; $p < 0.00001$) and in those who died from SARS-CoV-2 MD= −8.0195% CI: (−12.50, −3.51; $p = 0.0005$). The results of the study indicate that patients with VDD have an increased risk of developing severe disease OR=4.58; (95% CI: 2.24-9.35); $p =$ 0.0001; but they do not have an increased risk of dying OR=4.92; (95% CI:0.83-29.31); $p =$ 0.08).

The second main grouping included meta-analyses that examined the association between supplementation and severity.

The meta-analysis by **Szarpak et al. (2021)** included a total of 2322 individuals, 786 in the vitamin D supplementation group and 1536 in the control group. A lower 14-day mortality rate was associated with vitamin D supplementation compared with no supplementation (18.8% vs. 31.3%, respectively; OR=0.51; 95%CI:0.12–2.19;p=0.36).Moreover, VD supplementationwas associated with a lower in-hospital mortality rate (5.6% vs. 16.1%; OR=0.56; 95% CI: 0.23–1.37; $I^2 = 74\%$; $p = 0.20$), decreased ICU admissions (6.4% vs. 23.4%; OR = 0.19; 95% CI: 0.06–0.54; $I^2 = 77\%$; $p = 0.002$), and a reduced risk of mechanical ventilation (6.5% vs. 18.9%; OR = 0.36; 95% CI: 0.16–0.80; $I^2 = 0.48$; $p = 0.01$). In a meta-analysis by **Beran et al.(2022)**, the included studies all employed oral vitamin D supplementation protocols with highlyvariable dosages and durations. In SARS-CoV-2 patients, vitamin D supplementation was notassociated with a reduction in mortality RR=0.75; (95% CI: 0.46-1.23, p=0.25). Nevertheless, VD supplementation significantly reduced intubation rates RR=0.55, (95% CI:0.32-0.97,p=0.04) and the hospitalization rate MD= −1.26; (95% CI: 2.27, 0.25; p= 0.01). A subgroup analysis did not associate VD supplementation with a mortality benefit in patients receiving vitamin D pre or post SARS-CoV-2. A meta-analysis by **Tentolouris et al. (2021)** indicated that vitamin D supplementation did not reduce mortality in hospitalized patients with SARS- CoV-2 (386 deaths or 25.81%) compared to the treatment group (61 deaths or 10.46%). (testfor overall effect size using the random-effects model OR=0.597;(95%CI:0.318– 1.121; $p = 0.109$). However VD supplementation significantly reduced the need for admission to ICU in hospitalized patients with SARS-CoV-2 (test for overall effect size using the random-effects model OR= 0.326; (95% CI: 0.149–0.712; $p = 0.005$).

Rawat et al. (2021) showed that vitamin D did not reduce the mortality rate RR= 0.55,(95%CI: 0.22 − 1.39, $p = 0.21$) or the ICU admission rate RR= 0.20, (95% CI: 0.01–4.26, $p = 0.3$) or the need for invasive ventilation RR = 0.24, (95% CI: 0.01–7.89, $p = 0.42$). Based on the pooled analysis, vitamin D supplementation was not shown to significantly affect clinical outcomes in SARS-CoV-2 patients. **Niniazt et al. (2021)** analyzed four studies involving 259 patients, 139 of whom received vitamin D supplementation. In comparison with the control group, VD supplementation significantly reduced the mortality OR=0.264; (95% CI: 0.099–0.708, $p =$ 0.008). **Shah et al. (2021)** analyzed studies involving pooled data from 532 hospitalized patients, 189 receiving vitamin D supplementation and 343 receiving a placebo. They examined the rates of mortality and admission to the ICU due to SARS-CoV-2 between supplemented and not supplemented individuals. There was a statistically significant reduction

in the need for ICU in patients who underwent vitamin D supplementation as compared to those that did not receive vitamin D supplements OR= 0.36 (95% CI:0.210–0.626). There was significant heterogeneity, which was reduced by a sensitivity analysis. Regarding mortality, vitamin D supplements were shown to have a similar effect to placebo treatment/usual care OR = 0.93; (95% CI: 0.413–2.113; $p = 0.87$). In a pooled analysis of 11 studies by a meta-analysis, **Hariyanto et al. (2021)** showed that vitamin D supplementation may reduce the ICU admission rate OR=0.27;(95% CI:0.09–0.76, p=0.010). In addition, vitamin D supplementationreduces ventilator use and mortality rates OR = 0.34; (95% CI:0.16–0.72, $p = 0.005$). Based ona meta-regression analysis, vitamin D supplementation and mortality are associated with age OR = 0.37; (95% CI: 0.21–0.66, $p = 0.027$). **Pal et al. 2021** showed that the use of vitamin D in SARS-CoV-2 patients reduced ICU admission and mortality rates OR =0.41; (95% CI: 0.20, 0.81, $p = 0.01$) as well as reducing the risk of adverse outcomes OR=0.27; (95% CI: 0.08, 0.91, $p = 0.03$)

Lastly, the third group included the meta-analyses that examined the vitamin D status in both serum and supplements in relation to both the risk of infection and the severity of SARS-CoV-2 .

Bassatne et al. (2021) examined seven outcomes, mortality, ICU admission, invasive and non-invasive ventilation, hospitalization, time of hospital stay, disease severity and SARS-CoV-2 positivity from 31 observational studies. Provided support for the idea that supplementing with calcifediol may reduce ICU admissions related to SARS-CoV-2. However, in order to determine whether vitamin D supplementation is effective for preventing and treating SARS-CoV-2 related outcomes, results from ongoing trials are needed. In a primary analysis, there was a positive trend between having a serum 25(OH) D level < 20 ng/mL and increased risks of mortality, ICU admission, invasive ventilation, non-invasive ventilation, and SARS-CoV-2 positivity. However, these associations were not statistically significant. The following values were obtained: ICU admission RR=4,89 (95% CI: 0.54–44.26, $p = 0.16$), invasive mechanical ventilation RR=1.34 (95% CI:0.64–2.79 $p = 0.43$), Non-invasive ventilation requirement RR=1 .08; (95% CI:0.30–3.80) p=0.91, and SARS-COV-2 positivity status RR=1.35; (95% CI: 0.93–1.96 $p = 0.11$). The treatment of SARS-CoV-2 patients with high doses of vitamin D is not supported by solid evidence. **Petrelli et al.(2021)** associated VDDwith a higher risk of SARS-CoV-2 infection OR = 1.26; (95 % CI: 1.19–1.34; $p < 0.01$) and a greater disease severity OR = 2.6;(95 % CI: 1.84–3.67; $p < 0.01$) and higher mortality rate than those of non-deficient patients OR = 1.22; (95 % CI: 1.04–1.43; $p < 0.01$). **Chen et al. (2021)** two RCTs and eleven cohort studies were included in the study and found that VDD(< 20 ng/mL) or insufficiency (< 30 ng/mL) did not significantly increase the risk of infection with SARS-CoV-2 OR for 20 ng/mL=1.61, (95% CI:0.92–2.80, I^2= 92%) or the rate of death in the hospital OR for 20 ng/mL = 2.18 (95% CI:0.91–5.26, OR for 30 ng/mL=3.07 (95% CI: 0.64–14.78). An increase in serum vitamin D of 10 ng/mL was not associated with a significant reduction in the risk of SARS-COV-2 infection OR = 0.92 (95% CI: 0.79–1.08, $I^2 = 98\%$) or death OR= 0.65(95% CI:0.40–1.06, $I^2 = 79\%$). In additional vitamin D supplementation did not significantly decrease the rate of death OR=0.57 *($I^2 = 64\%$)* or ICU admission OR = 0.14 ($I^2 = 90\%$) in patients with SARS-CoV- 2. There were no significant decreases in the rates of mortality OR=0.57 ($I^2 = 64\%$) or ICU admission OR= 0.14 ($I^2 = 90\%$) in patients with SARS-CoV-2 who received vitamin D supplements.

Table 3: Association between serum vitamin D levels in terms of deficiency/insufficiency with risk of infection and/or risk severity, hospitalization, ICU admission, and mortality from SARS-CoV-2

Study	Study Locations	Cases/Subjects	Exposure to Vitamin D that Meta-Analysis Examined	Eligibility period	Heterogeneity	Main Results	Publication Bias	Risk of Bias Assessment within Studies	No. of Studies	Outcomes
Munshi et al. (2021)	US, Switzerland,China, Ireland, Belgium, and Indonesia	SARS-CoV-2 patients Mean VD levels was 21.9 nmol/L (n = 376)	VDD(< 20 ng/ml) or insufficiency (< 30 ng/ml)	2019 - 2020	1a. I^2 = 99.1%, (p < .001) 1b. I^2 = 0,00% With Radon effect models. 2.Comorbidities 2a. Heart failure 1.I^2 =0 % (p=0.906) 2b. Diabetes 1.I^2 = 0% (p=0.478) 2c. Hypertension 1.I^2 = 0% (p=0.970) 3d COPD 1.I^2 = 0% (p=0.954) Subgroups: American I^2 .-% (p=n/a) European I^2 =99.82% (p=0,00) Asian I^2 =97.20% (p=0.00)	1a Vitamin D serum level of 376 patients, was 21.9 nmol/L (95% CI:15.36–28.45). 1b.Patients with poor prognosis (n = 150) significantly lower serum levels of VD compared with those with good prognosis (n= 161), representing an adjusted standardized mean difference of −0.58 (95% Cl : −0.83 to −0.34, p < .001) 2.Comorbidities 2a. Heart failure (OR = 0.57, 95% CI: 0.28–1.15, p = 0.12) 2b Diabetes (OR =0.82, 95% CI: 0.35–1.92, p = 0.79),	No evidence of publication bias using Egger's test PE = 0.22. funnel plot is used to assess publication bias. However Studies <10.	N/A	n=6 total (n=5 retro, 1 case control)	1. SARS-CoV-2 Severity 1a.Vitamin D serum level in positive patients 1.b.Prognosis Poor vs good 2.Comorbidilites

						2c Hypertension (OR=1.21, 95% CI :0.28–5.11, p =0 .65), 1d COPD (OR = 0.77, 95% CI: 0.31–1.88, *p* =0 .57). Subgroup analysis for American (mean 22.91 nmol/L, CI:19,75-26.07) the highest vitamin D serum levels among Eur. studies (mean = 24.8 nmol/L, 95% CI :14.02–35.65) and Asian studies (16.8 nmol/L , 95% CI 5.19–28.59).				
Ben-Eltriki et al. (2021)	Iran, Italy, US, Turkey. Belgium, Spain, India, China , and Greece	SARS-CoV-2 patients (n = 3637)	vitamin Deficiency 25 (OH) D levels of <10 to <30 ng/ml.	2019–2021	High for all studie 1a. I^2 =92% (*P*<0,00001) Severity 1b. I^2=68% (*p* <0.0001) Mortality 1c. need mechanical ventilation I^2 =65% (*p*=0.001) 2a. dimer (mg-mL) I^2 =92% (*p*<0,00001)	1. A low vitamin D status increased the risk of developing severe SARS-COV-2 pneumonia 1a. (RR: 1.50; 95% CI: 1.10–2.05) 1b. risk of death (RR, 1.60 (95% CI, 1.10–2.32) 1c. (RR: 1.14; 95% CI, 0.87–1.50)	N/A	N/A	24 Observational studies n = 24 observational studies (Retrospective, cohort, observational single center study, review cross-	1. SARS-CoV-2 Severity 1a severity 1b mortality 1c. Need for mechanical ventilation 2. Cardiac biomarker (troponin and D-dimer) 2.c C-reactive protein

					2b. troponin ng/L levels I^2 =0% (p=0.55) 2.c C-reactive protein (mg/L) levels. I^2= 100% (p= 0,0001) 2.d interleukin-6 (pg/mL) levels. I^2 = 81% (p<0,0001)	2. Cardiac biomarker (troponin and D-dimer) levels tended to be lower in the vitamin D sufficient SARS-CoV-2 patients. Biomarkers of inflammation (CRP and IL-6) were significantly higher in patients with low vitamin D levels. (95%CI -0.26–05700.04, p = 0.09) 2b. troponin ng/L levels MD -3,26(-5,96,--0,57, p=0,02			sectional study, Retrospective case-control study Retrospective observational trial)	(mg/L) levels. 2d. interleukin-6 (pg/mL) levels.
Al Kiyumi et al. (2021)	UK Colombia, Israel, Florida, Belgium, USA, Russia, Ireland, Italy,South Korea ,Austria, Mexico, Germany, and Israel.	Patients with SARS-COV-2 (n = 254,936)	VDD(< 20 ng/mL) or insufficiency (<30 ng/mL)	2019–2020	1. N/A 2a.VDD severity I^2= 73%(p <0,00001) 2b. VDI severity I^2 = 8%, (p =0,23) 2c. Overall I^2 =67% (p=0,000) After sensitive analysis I^2 =23.7% (p=0.25) 2d High Vs low levels I^2 = 96% (p<0.0001)	1. higher prevalence of VDD and VDI in patients with SARS-CoV-2 (59.0% & 40.1%, respectivel) 2c VDD and VDI associations with the severity of SARS-CoV-2 symptoms OR = 3.38, (95% CI: 1.94–5.87, p < 0.0001). 2.d Lower level had severe symptoms SMD= −6.85, CI: −9.43–	non-significant risk of publication bias for the severity of symptoms (PE=0.071). However, was significant for mortality rate (PE=0.023) Funnel plots are listed.	Newcastle–Ottawa Scale (NOS) was Moderate were 36 studies 2 studies low and 3 studies had high risk	43 observational studies	1. SARS-CöV-2 Prevalence 2. SARS-CoV-2 severity 3. SARS-CoV-2 mortality

					3aVDD Mortality I^2=48%, (p=0,02) 3.b VDI mortality I^2= 0% (p =0.95) and VDD/VDI mortality Overall I^2 = 36% (p=0.06) After sensitive analysis VDI Fatality I^2= 0% (p=0,56)	−4.27, P <0.0 0001, 3. positive association between VDD or VDI & mortality was identified OR = 2.30, (95% CI: 1.47–3.59, p< 0.00001)				
Wang et al. (2021)	Belgium, India, Switzerland, Italy, China, Spain, Iran, UK, US, Korea, Austria, Germany, and Pakistan	SARS-COV-2 positive participants: (n = 2756)	VDD(< 20 ng/mL) or insufficiency (< 30 ng/mL)	2019–2020	1. Mortality rate 1a:OR= I^2 =30.5% *(p=N/A)* 1b:HR= I^2=11,6% *(p=N/A)* 2. Hospital admissions I^2 = 0% *(p=N/A)* 3. hospital stay I^2 = 89.6% *(p=N/A)* 4. ICU I^2 =83,1% *(p=N/A)*	1.Vitamin DD was associated with mortality rate: 1a OR= 2.47, 95% CI: 1.50–4.05; 1b HR=: 4.11 95% CI: 2.40–7.04) 2.Increased hospital admission rates: OR= 2.18, (95% CI: 1.48–3.21) 3. longer hospital stays (+0.52 days; 95% CI: 0.25–0.80) 4.no significant difference in ICU R:5,44 (95%CI: 0,38-78.42) Subgroup analysis based on cut-offs 2. The geographic location, and 3. The	Did not find a publication bias for mortality (no available data preside regarding *PE* or funnel plot However, the study was unable to statistically evaluate the other factors because < 10 studies	Newcastle–Ottawa Scale tool High Risk (n=13) Low Risk (n=3) Moderate risk (n=1)	17 observational studies	1. SARS-COV-2 mortality 2. Hospital admission 3. Length of hospital stay (days) 4.ICU admission

						altitude *(*too many data-available in supplementary)*				
Halim et al. (2022)	China, Italy, Spain, United States, Turkey	SARS-COV-2 patients n= 1424 severity n=1339 mortality	**(TNF-α, IL-6,) & VDD(<20 ng/mL) or insufficiency (< 30 ng/mL)**	2020-2021	1a. aTNF & Severity I^2=63% (*p*=<0,04) 1b.TNF-a &Mortality I^2=80% (*p*=0,008) 1.c IL-6 Severity .I^2=86% (*p*=<0,00001) 1d.IL-6 Mortality I^2=81% (*p*<0,000001) 2a Severity & SARS-COV-2 I^2=94% (*P*<0,000001) 2b.VDD mortality Cure I^2=75% (*p*=0,02) and VDD mortality adj I^2=66% (*p*=0,02)	**1a TNF-a** insignificantly increases the risk **severity** (aOR=1.0304,95%CI:0.8178-1.2983,*p*=0.80) but significantly the risk **1.b mortality** crude 1.0643(95% CI:1.0259-1.1036, *p*=0.009 **1c IL-6 s**insignificantly increases the risk **severity** (aOR=1.0284,,95%CI:01.0130-1.044,P=0,0003) And **1.d Ila-6& mortality** 1.0076,95%CI:1.0004-1.014, *p*=0,04, 2a**VDD& SARS-COV-2 VD** levels of **severe** SARS-COV-2 patients were not significantly lower than those of non-severe SARS-COV-2 patients (mean difference (MD) = −5.0232; 95% CI −11.6832–	N/A	Newcastle–Ottawa Scale tool Data only for 6 studies were moderate	48 studies 11 for vitamin D 1 case-control, 5 cross-sectional, 16 Cohort studies, and 26 retrospective cohort	**1. a TNF-α&severity 1b.TNF-a &Mortality 1c.IL-6** severity **and SARS-COV-2 1.**d il-6-a &**Mortality** **2. VDD and SARS-COV-2** a.Severity, b.Mortality

					1.6368; p = 0.14) **2b.VDD** SARS-CoV-2 Mortality insignificantly increased the risk of **mortality** from SARS-CoV-2 (**crude** OR = 1.1505; 95% CI 0.5299–2.4977; p = 0.72). VDD insignificantly increased the risk of mortality from SARS-CoV-2 adjusted (OR = 1.3827; 95% CI 0.7103–2.6916; p = 0.34)			
Oscanoa et al. (2021)	UK, Philippines, USA, Germany, Iran, Belgium, South Korea, Spain, Switzerland, Turkey, and China.	SARS-CoV-2 patients n = 2692	VDD(<20 ng/mL) or insufficiency (< 30 ng/mL)	2019–2020	1. severity I^2 = 83.3% (p = 0.000) 2. mortality. I^2 =81.2% (p = 0.000)	1. VDD releded with higher risk of SARS-CoV-2 1. Severity RR 2.00;(95% CI:1.47–2.71) **2. Mortality** rate (RR 2.45; 95% CI 1.24–4.84). Concentration of 25-hydroxyvitamin D 25 (OH) D influences the SARS-CoV-2 severity and mortality rates. **Subgroup analyses were** conducted to assess the effects of age, sex, and an alternative	N/A	Low risk of bias using the Newcastle Ottawa CocHR=ane risk of bias assessment tool. The average score for the NOS was 8.1 (range: 7-9).	23 studies (11 case-control, 5 cohort, and 7 cross-sectional observational studies)	1. Severity 2. Mortality

					25(OH) D cut-off value (< 30 nmol/L) separately. Severity risk was higher in people < 60 years of age (p = 0.040,)				
Ebrahimzadeh et al. (2021)	Kuwait, Saudi Arabia, UK, Germany, US, Turkey, and Italy	SARS-COV-2 positive participants n= 2208	VDD < 20 ng/ml) or insufficiency (< 30 ng/mL	2019-2021	Mortality I^2 =71.1% (p=0.008) fixed effect analysis was used for all subgroups.	vitamin D deficiency had a positive correlation with the risk of in-hospital mortality from SARS-COV-2 (OR=2.11; 95% CI: 1.03, 4.32 All subgroup analyses also showed inverse significant relationships between the serum vitamin D level and the risk of in-hospital mortality	N/A	Newcastle-Ottawa 3 out of 13 studies had a moldered bias, 10 out of 13 had a low bias	13 observational studies	SARS-CoV-2 Mortality
Teshome et al. (2021)	USA, Indonesia, England,Israel, Switzerland, Iran, China, Spain, Turkey, Belgium,and Saudi Arabia	Participants: n= 91,120	serum VDD Compared the risk of developing SARS-COV-2 infection among individuals with VDD Vs normal VD levels.	04.2020–12.2020	I^2 = 71.9% (p=0.0002) Subgroup analysis study design Cohort I^2 = 0,00% (p=0,58) I^2 = 75% Cross sectional (p=0,0002) I^2 = 85% Case control (p<0.0001)	VDD increased the risk infection SARS-COV-2 by 80% Vs to those with normal VD levels OR = 1.80; 95%CI: 1.72, 1.88) Subgroup analysis – the study design revealed that the pooled effect of VDD was 1.81 in case-controlled studies (OR = 1.81, 95% CI: 173-190)	No significant publication bias, according the Begg s (PB= 0.764)	Moderate JBI critical appraisal checklist Only 50>score were included	8 studies Systematic reviews,meta-analyses, 1 cross-sectiona,	Risk of SARS-CoV-2 infection
Liu et al. (2021)	UK, Israel, US, Switzerland, Iran, China, and Korea	SARS-COV-2 positive participant (n= 361,934) SARS-COV-2 negative	Deficiency or insufficiency of vitamin D in the serum	2019–2020	1.I^2=64.9% (p = 0.036) 2.I^2=89.6% (p =0,000) Subgroup analysis I^2=89,8% (p=0,000)	1.insufficiency /deficiency of vitamin D increased the risk of getting SARS-COV-2 (OR = 1.43, 95%CI .00 – 2.05. 2.The vitamin D levels were	Funnel plots and Egger regression tests revealed a significant publication bias.	Newcastle-Ottawa scale (NOS) showed a medium-quality with	10 case-control studies	Risk of SARS-CoV-2 infection 1.Low levels increased the risk 2. positive individual

		participants (n = 4178)				lower in SARS-COV-2 positive individuals than in SARS-COV-2 negative individuals (SMD = -0.37, 95% CI = -0.52 to -0.21). The subgroup analysis based on the 25 (OH) D measurement units (ng/mL and nmol/L) found positive results (nmol/L: WMD = -7.90, 95% CI = -13.41 to -2.38, I^2 = 89.8%; ng/mL: WMD = -5.85, 95% CI: -11.23 to -0.46, I^2= 93.6%) Subgroup analysis based on the 25 (OH) D measurement units (ng/mL and nmol/L) comparing the serum vitamin D levels among individuals with SARS-COV-2 positivity and negativity.	an average score of 7.7	s had lower vitamin d levels than negative individuals
Szarpak et al. (2021)	UK, Iran, Saudi Arabia, Italy, Spain, China, Republic of Korea, and Israel	SARS-COV-2 positive participants (n= 3197) SARS-COV-2 negative participant: (n= 11288)	VD levels in SARS-COV-2 Positive Vs Vegative	2019-2020	I^2= 99% (p < 0.0001)	SARS-CoV-2 negative patients had a mean Vitamin D level of 17.7 ± 6.9 ng/mL. T he level in SARS-COV-2 positive patients was 14.1 ± 8.2 ng/mL (MD = 3.93; 95% CI 2.84–5.02; I^2= 99%; p < 0.001 Low serum vitamin D levels were statistically significantly associated with an increased risk of SARS-COV-2 infection.	N/A	Rob tool 0–25% low risk and 25-100% moderate risk Moreover, the Robvis application was used to visualize the risk of bias assessments	13 studies (4 case control, 2 retro, 4 prospective cohort, 1 population-based study, 1 multi-center case control, 1 retro case control, 2 retro)	Risk of SARS-CoV-2 infection

Ghasemian et al. (2021)	UK, South Korea, Iran, US, Israel, China, Pakistan, India, Germany, Greece, Russia, and Italy	SARS-COV-2 positive participants (n = 11 901)	Vitamin D deficiency /insufficiency in serum Vitamin D sufficiency: 25(OH) concentration greater than 30 ng/mL. Vitamin D insufficiency: 25 (OH) D concentration of 20-30 ng/mL. Vitamin D deficiency: 25 (OH) D level less than 20 ng/mL.	2019 - 2020	I^2 =N/A in the forest plot	1.Patients with a VDDhad a 5 times higher chance of developing severe SARS-COV-2 (OR= 5.1, 95% CI, 2.6–10.3) than those with sufficient vitamin D 2.The odds of getting infected with SARS-CoV-2 were found to be 3.3 times higher among individuals with a VDD(95% CI, 2.5-4.3) 3. No significant association between vitamin D status and higher mortality rates was identified (OR= 1.6, 95% CI, 0.5-4.4).	Begg's and Egger's tests revealed a publication bias of (PB = 1.00; PE = 0.55) for VDDand SARS-CoV-2 infection and a bias of (PB = .12; PE = 0.14) for VDDand SARS-COV-2 severity. The biases for VDDand SARS-CoV-2 mortality were *PB*= 0.54; *P*E = 0.62	Studies had a low risk of bias According to the Newcastle-Ottawa Scale (NOS) Results of the quality assessment for studies entered into meta-analysis were fair.	23 studies, 17 observational studies, 6 meta-analyses.	1. SARS-CoV-2 Severity 2. SARS-CoV-2 Infection 3. SARS-CoV-2 Mortality
Pereira et al. (2020)	The UK, South Asian countries, Germany, Barcelona, Spain, USA, Iran, and South Korea	SARS-COV-2 positive participants: N = 8.176	prevalence of VDDin SARS-COV-2 patients	2020	1a V DD (<50 nmol/L) risk of infection. I^2 =**78.5%** (*p*=0,003) 1b Covid patients had lower concentrations	1a No association between VDDand a higher risk of SARS-COV-2 infection 1. (OR ¼ 1.35; 95% CI ¼ 0.80–1.88) *p* = 0.003 1b. However, the values of serum	Funnel plot of ten studies for the association between VDD and occurrence of several SARS-CoV-2 shows a	25% low and 75% high Research Triangle Institute Item Bank (RTI–Item Bank) scale	n=27 systematic reviews with 21 included in the meta-analysis (Retro n= 6, Retro Multi center n=1 Cohort, n= 8 Retro cohort n=3	1. the prevalence of VDD in severe cases of COVID 1a **high Risk** infection 1b SARS-CoV-2 and Values

					in the serum I^2 = **99.5%** (*p*=N/A) 2 severity I^2= 35.7%, (*p*=0,122) 3 hospitalization I^2 = 0.0% (*p*=0,87) 4 mortality. I^2=59.0% (*p*=0,045)	vitamin D in patients with SARS-COV-2 in relation to healthy individuals were low (WMD = −17.02, 95% CI = −29.61 to −4.43; 2. VDDled to more severe cases (65%), OR ¼ 1.64; 95% CI ¼ 1.30–2.09) than mild cases 3 The hospitalization rate was increased in individuals with VDD(OR ¼ 1.81, 95% CI ¼ 1.41–2.21) *p*=0.872 4.Mortality increased in individuals with VDD(OR ¼ 1.82, 95% CI ¼ 1.06–2.58)	satisfactory distribution. However, was not assessed for the remaining outcomes because it was it was not appropriate for the assessment of prevalence in meta-analyses		Cross-sectional n=4 Retro Cross-sectional n=1 Clinical retro. n=1 Population based n=1 Case series n=1)	serum in covid patients were higher than in healthy individuals. 2. SARS-CoV-2 severity 3. SARS-CoV-2 hospitalization 4. SARS-CoV-2 Mortality
Kazemi et al. (2021)	Turkey, UK, Switzerland, Spain Italy, USA, South Korea, China, Iran, and Israel	SARS-COV-2 positive participants: (n=13021)	Concentration of 25-hydroxyvitamin D (25(OH)D) in the serum	2019-2020	Evaluated using CocHR=ane's Q test, deriving its magnitude from the I^2 value. 1. risk of infection I^2=44.2 % crude	1.Higher risk of SARS-CoV-2 infection in individuals with VDD OR= 1,77; (95% CI: 1,24, 2,53) Crude And OR=1,75; (95% CI: 1,44, 2,13) Adj.	Egger's test, publication bias was evident in the comparison of SARS-CoV-2–positive and negative subjects (*p* = 0.002)	low for all studies Newcastle–Ottawa Scale-cohorts Scale score=3-6 CocHR=ane risk-of-bias tool - RTS	N=39 total (Case controls n=10, cross-sectional designs n=19, randomized controlled trials n=22 retro cohorts, 4 descriptive studies, and 2 quasi-	1. SARS-CoV-2 infection 2. SARS-CoV-2 Severity 3. SARS-CoV-2 Mortality

					(*p*=0,167) OR And I^2 =33.0% infection risk (*p*=0,20) Adjusted 2. severity I^2 = 0.0% Effect size (*p*=0,001) and I^2=90.8% (*p*=0,46) crude 3. mortality I^2 =47.9% *p*=0,104, ES, MLR And I^2 = 84% crude *p* ≤ 0,001)	2. Higher severity in the VDD group OR= 2.57; (95% CI: 1,65, 4,01) adj. and crude OR= 10,61; (95% CI: 2,07, 54,23) 3 Indicated a significant association of VDD with mortality OR= 2,62; (95% CI: 1,13, 6,05) crude and adjusted studies that used the Cox survival method HR=: 2.35; (95% CI: 1.22, 4.52) indicated a significant association with VD, while in adjusted studies that used a logistic regression, no relation was observed OR= 1.05; (95% CI: 0.63, 1.75)	no publication bias was identified in the comparison of severe and less-severe SARS-CoV-2 patients (*p* = 0.60); however, a small deviation towards an WMD of ∼−5 and an SE ≈2 was observed in a funnel plot		experimental studies.	
Chiodini et al. (2021)	Germany, UK, Ireland, Italy, US, Spain, Russia, Iran, Netherlands, Mexico, Algeria, India, China,	n=1,403,715 Individuals	Vitamin D status insufficiency <75, deficiency <50 or severe deficiency <25 nmol/L	2020	1a severe VDD <25 nmol/L I^2 =83% (*p*=0,094) 1b VDD <50 I^2 =72% (*p*=0,09)	1a.1 ICU was associated with severe VDD OR= (95%CI: 2.63, 1.45–4.77) 1a2.b VDD, OR= (95%CI:	The study has no publication bias. The Egger's test estimation was used to evaluate the publica	Newcastle-Ottawa scale (NOS) 35 low risk 6 high 16 moderate	54 studies n=49 fully-printed and n=5 pre-print publications, 28 Props. and 26 Retro)	1a,b,c SARS-CoV-2 Severe ICU admission 2 a,b,c SARS-CoV-2 Mortality Risk

and Greece	1c VDI<75 I^2 =44% (*p*=0,06) 2.Mortality 2.a related death severe VDD<25 nmol/L) I^2 =42% (*p*=0,33) 2b VDD <50 2c I^2 =70% (*p* 0.001) 2c VDI <75. I^2 =77% (*p*=0.10) 3. Infection 3a I^2 =79% (*p*=0.10) severe deficiency <25 nmol/L) 3b deficiency <50 I^2 =88% (*p*=0.03) 3.c insufficiency <75 I^2 =78% (*p*=0,59) 4 LOS 4a.I^2 =57% (*p*=0,40) severe deficiency <25 nmol/L) 4b.I^2 =60% (*p*=0.25)	2.16, 1.43–3.26) and 1c VDI OR= 2.83, (95%CI: 1.74–4.61). 2 Mortality was associate2.a1 with Severe VDD OR= 2.60, (95%CI: 1.93–3.49) and 2b2 VDI OR=1.84(95% CI: 1.26–2.69) and b3 OR 4.15,(95%CI: 1.76–9.77) 2a. Infection, SARS-CoV-2 infection OR= (95% CI: 1.68, 1.32–2.13; 1.83, 1.43–2.33; 1.49, 1.16–1.91, respectively) 4 Hospitalization OR (95%CIs 2·51, 1.63-3.85; 2.38, 1.56-3.63; 1.82, 1.43-2.33) respectively	tion bias presence ICU *p* =0.816 <25 nmol/L. *p*=0.066. <50 nmol/L Insufficiency <75 *p*=0.011 Death *p*=0,110 <25 nmol/L *p*=0.039 <50 nmol/L *p*=0.627 Insufficiency <75	3 a,b,c SARS-oV-2 Infection-susceptibility 4 SARS-CoV-2 related Hospitalization

					deficiency <50 4c I^2 =0% insufficiency <75					
Kaya et al. (2021)	Iran, Spain, US, UK China, Korea, Israel, Turkey, Switzerland and and Greece	SARS-COV-2 positive participants: (n=205,869)	Vitamin D levels– Serum (25(OH) D < 20 ng/mL or 50 nmol/L)	2019-2021	1. Infection I^2=85% (p<0,001) 2. Severity I^2=92% (p<0,001) 3. Mortality I^2 = 83% (p<0,001)	1.The risk infection of SARS-COV-2 was higher in patients with low levels of vitamin D where1.64 times more likely to contract covid19 (95% confidence interval CI: 1.32 to 2.04; *p*< 0.001). 2.Patients with low serum levels of vitamin D (below 20 ng/mL or 50 nmol/L were 2.42 times (95% CI, 1.13 to 5.18; *p*= 0.022) more likely to have severe SARS-COV-2 . 3. Mortality was not affected by low vitamin D OR, 1.64; 95% CI, 0.53 to 5.06, *p*= 0.390	There was no publication bias in the 5 studies according to the Egger's test (*p*=0.911). The Egger's test detected a publication bias in 1 of the meta-analyses conducted in this study. The trim-and-fill adjustment method was performed.	Low Newcastle-Ottawa Scale (NOS) 17 studies poor 1 fair 5 good	21 studies were included in the meta-analysis (of 26 unclouded in systematic review) Cross-sectional=6 Case-control=10 Cohort=9	1. Infection 2. Severity 3. Mortality
Akbar et al. (2021)	China and UK	n = 999,179 SARS-CoV-2 patients	Low serum 25-OHD level	2019 - 2020	Rate of SARS-COV-2 1. Infectio	SARS-COV-2 1. infection rates increased	Funnel plot was asymmetrical	A low Newcastle-Ottawa	14 studies (8 Retrospective observatio	1. Infection rates

	Cut-off point ranging from 20 to 30 ng/mL	n I^2= 92.6% (p<0,001) 2. Disease severity I^2= 55.3% 3. Mortality I^2 = 83%	in patients with low serum Vitamin D levels compared to the control group OR = 2.71 (95%CI: 1.72- 4.2) *p* < 0.001). 2. Patients with low serum 25-OHD had a greater disease severity OR = 1.90 (1.24-2.93), *p* = 0.003) than the control group. 3. The mortality rate was higher in the Low serum 25-OHD group OR = 3.08 95% CI: 1.35-7.00), *p* = 0.011) than in the control group. 4. Meta-regression analysis showed that the association between low serum 25 (OH) D and mortality was affected by male gender OR = 1.22 (1.08-1.39), *p* = 0.002), diabetes OR = 0.88	for mortality, severity, and susceptibility. The Egger's test indicated significant small-study effects for severity (*p* = 0.047) and mortality (*p* = 0.046). There was no indication of small-study effects for susceptibility (*p* = 0.615).	Scale (NOS) Severity was identified in 42% of individuals, while Mortality occurred in 24% of patients involved in the analysis. The retrospective design of the studies was considered a potential source of bias.	nal, 2 Observational, 2 Prospective observational, and 2 Cross-sectional).	2. Severity 3. Mortality

						(0.79-0.98), p = 0.019.				
Varikasuvu et al. (2022)	Spain, India, Saudi Arabia and Mexico	SARS-CoV-2 patients n = 551	RCTs on the association between Vitamin D intervention and the SARS-COV-2 outcome compared with the non-vitamin D groups (57 in intervention and 58 in placebo arms) with VDDat baseline (<20 ng/mL), despite achieving a sufficient status (30 ng/mL)	2019-2020	0.I^2 =48% p=0.03 1. I^2 = 52% severity p=0.06 2. I^2 = 0% positivity p=0.78 3. I^2 = N/A seropositivity. 4. I^2= 33% mortality. p=0.21	0. Severity Overall (RR = 0.60, 95% CI 0.40 to 0.92, Z = 2.33, p = 0.02) severity RR=0,465% (CI:0,23-0,93) 2. RT-CR positivity was significantly decreased in the intervention group as compared with the non-vitamin D groups (RR = 0.46, 95% CI 0.24 to 0.89, Z=2.31, p=0.02). 3. Vitamin D intervention was effective for reducing the SARS-COV-2 relative risk, RR = 0.60, 95% CI 0.40 to 0.92, Z=2.33, p=0.02) 4. Mortality rate RR = 0.78, 95% CI 0.25 to 2.40, Z=0.66, (p=0.02)	No publication bias. The funnel plot assessment with Begg's (PB = 0.17) and Egger's tests (PE = 0.14) on all the outcomes across all RCTs. p>1.	CocHR=ane Risk of Bias tool. The overall bias of the included studies: "some concerns" related to randomization, blinding, outcome analysis and reporting of results. Only one of the 6 studies had a low level of bias and the other had a moderate level	6 RCTs	0. Severity overall 1. Severity 2. COVID RT-PCR positivity 3. Seropositivity 4. Mortality
Grafa et al. (2021)	Russia, Italy, South Korea,	SARS-CoV-2 patients and	25 (OH) D levels as a continuo	2019-2021	High 1. I^2 =95%	Patients with SARS-CoV-2	N/A	All studies	30 studies Retros. n=1	1. Risk of Covid 19

	India, UK, China, Austria, Turkey, Germany, Spain and Greece	Individuals n=37.9120	us variable in SARS-CoV-2 positive and negative patients.	vitamin D levels (p<0,0001) 2. I^2 =98% severity (p<0,0001) 3. I^2 =86% mortality (P<0,0001) **Subgroups** a.)VD<20ng/ml (I^2 =81%, p<0,00001), no b).VD<12ng/ml, (I^2=0%, p=0,95) c. VD<10ng/ml was not applicable for because of only one study.	infection had 1. Significantly lower levels of serum 25 (OH) D than negative patients MD -3.99 (-5.34, -2.64); (p <0.00001) 2. Patients with severe disease had lower 25 (OH) D levels [MD -6.88 (-9.74, -4.03) p <0.00001). 3. Those who died of SARS-CoV-2 MD -8.01 (CI:-12.50, -3.51); p = 0.0005) 4. Risk for SARS-CoV-2 was high in patients with VDD OR=4.58 (CI:2.24, 9.35; p <0.0001)	were judged to be of fair quality after analysis.	Retro. Mult.n=1 Pilot n=1 Prosp.Cohort=5 Retro. Observ. n=1 Population based study n=1 Prosp. observational study =3 Observ. cohort study n=4 cross sectional =1 Case-control study=7	2. Severity 3. Mortality

Table 4 : Association between supplements Vitamin D with risk of infection and/or risk severity, hospitalization, ICU admission, and mortality from SARS-COV-2 .

Study	Study locations	Cases/Subjects	Exposure to Vitamin D that Meta-Analysis Examined	Eligibility Period	Heterogeneity	Main Results	Publication Bias	Risk of bias assessment within studies	No. of Studies	Outcomes
Szarpak et al. (2021)	Spain, France, Italy, Brazil, Singapore	N= 2.322 patients, 786 in the vitamin D supplementation group and 1536 in the control group. 14 days.	Vitamin D supplements and positive vs negative dichotomous outcomes.	2019 - 2021	1a.ICU Admission I^2 =0% (*p*=0.48) 1b. I^2 = 0.48% (*p* = 0.01) 2.Mortality I^2 = 74% (*p*=0,002)	1 The need for ICU care was statistically lower in the group in which vitamin D was administered orally compared to the control group without vitamin D supplementation (6.4% vs. 23.4%; OR = 0.19; 95% CI: 0.06–0.54; I 2 = 77%; *p* = 0.002). 1b. Vitamin D supplementation in patients with SARS-COV-2 compared to patients who did not receive vitamin D was associated with less frequent use of mechanical ventilation (6.5% vs. 18.9%; OR = 0.36; 95% CI: 0.16–0.80). 2.in-hospital mortality in the vitamin D vs. non-vitamin D groups show a significant difference in mortality rate, 5.6% vs. 16.1%. Vitamin D supplementation lowered in-hospital mortality (5.6% vs. 16.1%; OR = 0.56; 95% CI: 0.23–1.37)	N/A	Low The RoB 2 tool, Robvis, was used in both randomized trials, the overall risk of bias was rated as low. In the non-randomized trial, 3 studies were rated as low and 3 were rated as having a moderate risk of bias.	In total, 8 Randomized studies were included in the review (n = 2) and 6 non-randomized studies were included	1. ICU admission (need for mechanical ventilation, radiological improvement, and secondary infection incidence. 2.Mortality rate. (14-day rate and in-hospital mortality)
Beran et al. (2022)	Spain, Italy and France	SARS-COV-2 positive participants: (n = 3497)	Vitamin D supplements were investigated using tHR=ee individual micronutrient supplements: vitamin C, D, and zinc	2019-2022	1. I^2= 77% p<0,00001) Mortality 2.. I^2 =48%(,p= 0,10) intubation rates 3. I^2 = 0% LOS	1. No association between vitamin D supplementation and a reduced mortality rate (RR 0.75, 95% CI 0.46e1.23, *p* ¼ 0.25). 2a. However, vitamin D supplementation	Asymmetry in the funnel plots showed the presence of a publication bias. An additional Egger's regression analysis demonstrated a statistically significant	Low for all studies	13 studies (4 RCTs and 9 observational studies)	1. Mortality and supplement 2. Intubation ratents. 3. Length of hospital stay.

					Subgroup analysis I^2=79%, (*p*=0,001) pre-covid diagnosis and diagnosis post-COVID-19 (I^2 = 69%, (*p*=0,001 %)	was associated with a significant reduction in the intubation rate. Reduced hospitalization rate (RR 0.55, 95% CI 0.32e0.97, *p* 1⁄4 0.04) and LOS (MD -1.26; 95% CI -2.27, 0.25; *p* 1⁄4 0.01). 2b. LOS (MD -1.26; 95% CI -2.27, 0.25; *p* 1⁄4 0.01, I2 1⁄4 0%. The subgroup analysis showed that vitamin D supplementation was not associated with a mortality benefit in patients receiving vitamin D pre or post SARS-COV-2 diagnosis.	publication bias (*p* < 0.047).			
Tentoloouris et al. (2021)	India, UK, Italy and Singapore	SARS-COV-2 positive participants: (n=2078)	Vitamin supplement vs. no supplement	2019 - 2021	1 Mortality I^2 = 62.4% (*p*=0,006) 2.ICU I^2 = 60% (*p*=0,028)	1. The mortality rate was lower in SARS-CoV-2 patients treated with vitamin D supplements (386 deaths or 25.81%) than the treatment group (61 deaths or 10.46%). OR= 0.597; (95% CI: 0.318–1.121; *p* = 0.109). 2. 12.91% of patients in the treatment group were admitted to the ICU compared to 26.27% in the non-treatment group OR=0.326;(95% CI: 0.149–0.712; *p* = 0.005)	Egger's and Begg's tests did not identify any publication bias (*p* < 0.05)	High 1. CocHR=ane risk-of-bias for randomized trials (RoB 2 tool 2. The ROBINS-I tool was used for the assessment of risk of bias of non-randomized trials. Presence of insignificant inconsistencies (minimum CI overlap and large variation in approximation effects) with no explanation. GRADE characterized as "very low" for both outcomes.	9 studies (2 RCTs and Prospective observational studies).	1 Mortality 2. ICU
Rawat et al. (2021)	India, Brazi, Spain, &	SARS-COV-2 positive participants: n=467	VDD/infancy The follow up period ranged	2019-2021	1. Mortality I^2 = 58% (*p*=0,07)	1. Vitamin D did not reduce mortality RR 0.55, (95%	N/A	Low Risk of bias graph showed	5 studies 3 RCTs and 2 Quasi-	1. Mortality 2. Invasive ventilation

	Franc e.		from 7–37 days.	2. Invasive ventilatio n I^2 =91% (*p*=0,0007) 3. ICU admission I^2 =89% (*p*=0,003) 4.N/A	CI:0.22 to 1.39, *p* = 0.21) 2. neither the need for invasive ventilation RR=0.24, 95% CI 0.01-7.89, *p* = 0.42) 3. no significant effect on the admission rate RR 0.20,95% CI: 0.014.26, *p*= 0.3) 4. Only one study evaluated all inflammatory markers, like fibrinogen, ferritin, d-dimer, CRP, and a significant reduction in fibrinogen values was shown (change of fibrinogen −0.64 (−1.41 to 0.11) in the intervention group vs. 0.06 (0.01–0.51) in the control group). The rest of the values were insignificant. Due to the paucity of data, the authors were unable to include quantitative data for two markers, d-dimer and CRP, so only qualitative data were taken from two studies (total 277 subjects, n = 135 for intervention and n = 142)		0-75%, indicating a low risk of bias and 25%, indicating an unclear result. The risk of bias summary was based on the CocHR=an e Systematic Review Guidelines The level of evidence as qualified using GRADE was low	experimen tal studies	3.ICU admission 4. Changes in inflammatory markers
Nikniaz et al. (2021)	Franc e, India, and Spain	SARS-COV-2 positive participant s: (n=259)	Vitamin D supplement ation Hydroxychl oroquine, and Corticoster oids (single-dose, oral route, 80,000 IU for one day), and 1 of the vitamin D deficient SARS-COV-2 patients (oral route,	2019 - 2020	Q = 1. 514, df = 2, I^2 =0.000, (*p* = 0.469) Mortality.	1. VD supplementation was associated with a significant reduction in the odds of mortality, compared with the control group (pooled OR =0.264, (95% CI: 0.099-0.708, *p* = 0.008).	The study did not refer to the publication bias.	All studies had a Low risk Joanna Briggs Institute (JBI) Critical Appraisal Tools for (RCTs) and quasi-experiment al studies. Most studies were of good quality.	4 studies (2 RCTs and 2 Quasi-experimen tal studies).	1.Mortality

			60,000 IU for 7 days Treatment goal 25 (OH) D > 50							
Shah et al. (2021)	Spain and Brazil	SARS-COV-2 positive participants: (n=532)	Vitamin D supplementation vs. standard of care or placebo	2019 – 202 0	Q statistics (significant at $p < 0.10$) and 1. ICU I^2=83% (p=N/A) 2.Mortality I^2=22%; (p= 0.27)	1. Patients supplemented with vitamin D had lower ICU requirements (p<0.0001) compared to those on placement or with a usual treatment odds ratio: 0.36; 95% CI: 0.210-0.626). 2.In case of mortality, vitamin D supplements were associated with comparable findings to the placebo treatment/usual care (odds ratio: 0.93; 95% CI: 0.413-2.113; p=0.87).	The Begg's and Egger's tests indicated the absence of any significant publication bias (p > 0.05). The funnel plot illustrated a satisfactory distribution of the studies 1.ICU Begg's tests p = 0.1172 Egger's tests Egger's tests p = 0.2538 2.mortality Begg's tests = p = 0.1172 Egger's tests =p = 0.1381	CocHR=ane tool-quality of included studies was reasonably fair, as all tHR=ee studies had a low risk of bias	3 studies	1. ICU requirement 2. Mortality.
Hariyanto et al. (2021)	Not identified	SARS-CoV-2 positive participants: (n=2265)	VD supplementation vs. standard of care or placebo	2019 - 2021	1. ICU admission I^2 = 70% *(p*=0,010) 2. Need for mechanical ventilation I^2= 61% (p=0,02) 3.Mortality I^2= 50% *(p*=0,03) meta-regression (Age, by gender hypertension, diabetes and corticosteroids)	1. Vitamin D supplementation reduced the care unit admission rate (OR 0.27; 95% CI: 0.09–0.76, p = 0.010). *2.*Need for mechanical ventilation (OR 0.34; 95% CI: 0.16–0.72, p = 0.005) and *SARS-COV-2* mortality (OR 0.37; 95% CI: 0.21–0.66, p < 0.001 Meta-regression suggested an association between vitamin D supplementation and mortality was affected by age (p = 0.027), meaning that older people will gain a greater protective effect against mortality in comparison with younger people. The association between vitamin D supplementation and mortality was not affected	Begg's tests and Mazumdar rank correlation the test did not identify any risk of publication bias	Low The Newcastle–Ottawa Scale was used to assess the quality of the cohort studies and case-controls. The studies were of good quality. Good (7 or 8) Joanna Briggs Institute Critical Appraisal tool -case control studies (all high quality) Jadad scale assessment of the quality of clinical trials. 1 study High quality 2 Moderate quality	11 studies (Cohort=5 case-control = 2, cross-sectional = 1 and randomized or non-randomized clinical trial = 3)	1. ICU admission. 2. Need for mechanical ventilation 3. Mortality

						by gender (p = 0.191); hypertension (p = 0.566); diabetes (p = 0.608); or the use of corticosteroids (p = 0.070)				
Pal et al. (2021)	Not identified	Positive SARS-CoV-2 subjects (n=2933)	Vitamin D supplementation vs. those not receiving the treatment.	2020-2021	1. ICU and/or mortality) in patients with SARS-CoV-2 as compared to non-use of VD I^2 = 66% mortality (p=0,001) 2. SARS-CoV-2 risk of admission I^2 = 80% (p=0,003) **Subgroups** (adj) of VDS on clinical outcomes ICU and mortality as compared to non-use of VD expressed either pooled as OR a I^2 = 74% (p=0,0007)or pooled hazard ratio b I^2 =12% (p=0,29)	1.ICU admission and mortality (OR 0.41, 95% CI: 0.20, 0.81, p = 0.01, I2 = 66% 2.VD reduced the risk of adverse outcomes (pooled OR 0.27, 95% CI: 0.08, 0.91, p = 0.03)	The random effect model was used to assess the publication bias. 0.41, 95% CI : 0.20, 0.81, p = 0.01	The Newcastle–Ottawa Scale (NOS) was used to assess the quality of observational studies. (p < 0.05) The CocHR=ane Collaboration instrument was used to assess the risk of bias for RCTs. The overall risk of bias was low	13 (10 observational, 3 RCT studies)	1. SARS-CoV-2 ICU/mortality 2. SARS-CoV-2 ICU admission

Table 5: Association between vitamin D levels in serum **and** supplements examined both the risk of infection and/or risk severity, hospitalization, ICU admission, and mortality from SARS-CoV-2.

Study	Studies Location	Cases/ Subjects	Exposure to Vitamin D that Meta-Analysis Examined.	Eligibility period	Heterogeneity	Main Results	Publication Bias	Risk of Bias Assessment within Studies	No. Studies	Outcomes
Bassatne et al. (2021)	Iran, Russia, Italy, Spain, Turkey, China, India, Pakistan, Greece, France, US, UK, Belgium, and Singapore	Positive SARS-CoV-2 subjects (n=8.209) Age range 42 and 81	1. Vitamin D supplementation 2. VDD (< 20 ng/ml) or insufficiency (< 30 ng/ml) The included trials administer vitamin D doses of 357 to 60,000 IU/day, from one week to 12 months.	2019 -2020	1.I^2 = 76% (*p*=0.0004) mortality 2.I^2 = 85% (*p*=0,001) ICU admission 3.I^2=0% (*p*=0.96) invasive requirement for mechanical ventilation or I^2 =23% (*p*=0.25) non-invasive requirement for ventilation 4.hospitalization (N/A) 5. I^2=0% (*p*=1.00) time of hospital stay 6.I^2 = 77% (*p*=0,04) 7.I^2 = 76% (*p*=0,02) positivity	1. SARS-CoV-2 mortality (RR:2.09 95%CI 092-477 p=0,08) Primary analysis, there was a positive trend between serum 25 (OH) D level <20 ng/ml and an increased risk of mortality, ICU admission, invasive ventilation, non-invasive ventilation or SARS-CoV-2 positivity. However, these associations were not statistically significant. 2.ICU admission RR: 4,89 95%CI:4.89 (0.54-44.26 p=016) Mean 25 (OH) D levels was 5.9 ng/ml (95% CI −9.5, −2.3) 3. Invasive mechanical ventilation RR: 1.34 (95%CI0.64-2.79 *p*=0.43) Non-invasive ventilation requirement RR : 1.08 (95% CI:0.30-3.80 *p*=0.91) 4. Hospitalization did not conduct a meta-analysis for this outcome	N/A Any subgroup analyses or publication bias assessment because of the limited number of available studies for every outcome of interest GRADE	NOS + CocHR=ane tool 1. Cross-sectional studies – high risk of bias for all studies and outcomes, 1 moderate 2. Control studies 4 low, 3 high risk 3. Cohort studies 19 low risk 20 high, 1 moderate 4. All of tHR=ee RTCs was unclear using the CocHR=ane risk of bias tool.	34 Studies 31 observational studies 3 RCTs	1 Mortality. 2. ICU admission 3. Invasive mechanical ventilation requirement-Non-invasive ventilation requirement 4 Hospitalization, 5. Time of hospital stay in days 6.Disease severity 7. Positivity rate.

						because of heterogeneity in the cutoffs used for serum 25 (OH) D levels. 5. Time of hospital stay Combining their data (n = 379), showed no significant difference in length of hospital stay between SARS-COV-2 patients with 25(OH)D < 30 ng/ml compared to those with more desirable levels (MD = 0, 95% CI:−0.97, 0.97 6.Disease severity cutoff for 25 (OH) D levels varied between studies; could not pool results from all studies RR = 3.0, (95% CI:9 0.19–48.2) 7 .SARS-CoV-2 positivity status RR1.35 (95%CI0.93-1.96, p=0.11) significantly lower in SARS-CoV-2 positive, compared to negative patients.			
Petrelli et al. (2021)	Iran, Saudi Arabia, France, Cyprus, Italy, Spain, Belgium US,	SARS-CoV-2 patients (n=612, 60)	1 vitamin D supplementation 2 VDD (< 20 ng/ml) or insufficiency (< 30 ng/ml)	2019 - 2021	1 I^2 = Not provided for risk Infection 2. Severity I^2=87% (p<0,0000)	1. VDD group had a higher risk of SARS-COV-2 infection compared with individuals sufficient OR = 1.26; (95 % CI: 1.19–1.34; P < .01)	The funnel plot shows a minimal risk of publication bias for infection (*PE* = 0.04)	8 out of 43 eligible studies were at low risk of bias, whereas 35 out of 43 were at moderate risk of bias, acco	43 studies reviewed, including 26 Retrospective studies, 5 Prospective studies, 4 Case controls, 3 Cross sectional	1. infection 2. Severity(hospitalization,mortality)

	Turkey, India, China, Greece, Asia, and Israel					2.VDD worse severity OR = (2.6;95 % CI: 1.84–3.67; P < .01) and higher mortality in non-deficient patients OR = 1.22; 95 % CI: 1.04–1.43; *p* < .01)		rding to the NOS scale.	and 3 Observational studies and 1 Registry data.	
Chen et al. (2021)	UK Biobank, University of Chicago Medicine, Medical university Hospital of Heidelberg, Boston University Medical Centre, Hospital Policlinic of Bari, UF health center US National clinical laboratory, Abu Dhabi, or Rashed hospital in Dubai, turkey Health Sciences University	SARS-CoV-2 participants (n=536, 10)	Vitamin D supplements & Vitamin in serum categorical analysis revealed that VDD(< 20 ng/ml) or insufficiency (< 30 ng/ml)	2019-2021	1. Mortality Supplement I^2 =64% (*p*=0,009%) supplements 1a mortality as categorical I^2 =79% (*p*=0,008) b. as continuous I^2=66% (*p*=0,09) 2. ICU admission I^2= 90% (*p*=0.001) 3a. infection supplements as categorical I^2 = 98% (*p*<0.0000) b.as continuous variable I^2 =92% (*p*<0,000001)	1.Vitamin D supplements did not significantly decrease death OR= 0.57, (95% CI: 0.04–7.78) 2. ICU admission OR= 0.14, 95% (CI: 0.00–4.90) in hospitalized patients with SARS-CoV-2 . UCU (p= 0,28) death (p= 0,67) When vitamin D level was analyzed as a continuous variable, each 10 ng/ml increase in vitamin D level was not associated with a significant decreased. 3. VDD(< 20 ng/ml) or insufficiency (< 30 ng/ml) was not associated with a significant increased risk of SARS-COV-2 infection (OR for < 20 ng/ml: 1.61, 95% CI: 0.92–2.80) Risk of SARS-COV-2 inflection (OR= 0.92, 95% CI: 0.79–1.08, or death (OR= 0.65, 95% CI: 0.40–1.06)	Publication bias was not assessed because of the limited studies (n < 10).	CocHR=ane risk of bias tool. The overall quality of the included studies was assessed with the Newcastle-Ottawa quality assessment scale (NOS), and an NOS score ≥ 6 was considered high quality + GRADE	13 studies, (11cohort studies and 2 RCTs)	1. Mortality and supplements 1a mortality as categorical b. as continuous 2. ICU admission supplements 3. Infection a)as categorical variable b)as continuous

B.2.5 Quality Synthesis of Meta-Analyses

In order to answer the research questions, we synthesized the 29 eligible meta-analyses into three main groups (Tables 6-8). When vitamin D was examined in the serum, the first group included meta-analyses that examined normal/high levels versus deficiency or insufficiency in relation to severity and the rate of infection. The second group included meta-analyses that examined vitamin D supplementation versus no supplementation when vitamin D exposure was associated with severity, risk of infection, or both. The last group included the meta-analyses that examined vitamin D exposure in both serum and as supplements.

The first group consisted of seven meta-analyses that examined the relationship between vitamin D deficiency/insufficiency versus sufficiency in relation to disease severity (hospitalization, death, intubation, respiratory support) (Munshi et al. (2021); Ben-Eltriki et al. (2021); Al Kiyumi et al. (2021); Wang et al. (2021); Halim et al. (2022); Oscanoa et al. (2021); Ebrahimzadeh et al. (2021).

Based on six out of the seven meta-analyses, vitamin D deficiency/insufficiency/low serum levels/sufficiency is significantly associated with disease severity (n = 5), mortality (n = 5), mechanical ventilation (n = 1), and treatment in the ICU (n = 1). Only the meta-analysis by Halim et al. (2022) found that level of vitamin D was not significantly lower than in those without severe disease and the mortality risk of SARS-CoV-2 patients is insignificantly inceased by vitamin D deficiency. (Table, 6a)

Regarding the subgroups of individual meta-analyses, two of the seven meta-analyses examined the comorbidities and ethnic and cardiac biomarkers. The meta-analysis by Munshi et al. (2021) showed low proportions of comorbidities (heart failure, diabetes, hypertension, COPD) across the included studies, with congestive heart failure being the most frequent comorbidity, followed by diabetes, hypertension, and chronic obstructive pulmonary disease (COPD). Regarding the ethnic subgroups assessed American, European, and Asian the highest vitamin D serum levels were found among European individuals and the lowest values were found among Asians.

Two studies out of seven investigated the association between vitamin D levels and Biomarkers.The Ben-Elriki et al. (2021) pooled 8 studies with cardiac biomarkers (troponin and D-dime) and inflammatory (CRP and IL-6) biomarkers, and found an association between vitamin D insufficiency and elevated inflammatory and cardiac biomarkers. On the other hand the pooled meta- analyses by Halim et al (2020) found that TNF-α is insignificantly associated with SARS-CoV-2 severity, however significantly associated with SARS-CoV-2 mortality.The IL-6 significantly increases the risk of SARS-CoV-2 severity and mortality, but the IL-6 is an independent prognostic factor towards SARS-CoV-2 severity and mortality. Further meta-analyses required to identify this finds.

Table 6: Association of SARS-CoV-2 severity in serum vitamin D levels-deficiency/insufficiency.

No	First Author	Severity	Mortality	Need Mechanical Ventilation and or ICU	Biomarkers
1	Munshi et al. (2021)	+	N/A	N/A	
2	Ben-Eltriki et al. (2021)	+	+	+	+
3	Al Kiyumi et al. (2021)	±	+	N/A	
4	Wang et al. (2021)	+	+	N/A	
5	Halim et al. (2022)	-	-	N/A	-
6	Oscanoa et al. (2021)	+	+	N/A	
7	Ebrahimzadeh et al. (2021)	N/A	+	N/A	

+positive association, -no significant association ± moderate association.

The meta-analyses that examined the serum level of vitamin D included the risk of infection (positive or negative) based on serum deficiency/insufficiency (n = 3) summarizing as second subgroup. The serum level of vitamin D was associated with the infection risk. (Teshome et al. (2021), Liu et al. (2021) and Szarpak et al. (2021)).

Table 7: Risk of SARS-CoV-2 infection in individuals with serum vitamin D deficiency/insufficiency.

No	First Author	Association with Risk of Infection	No Association with Risk of Inflection
1	Teshome et al. (2021)	+	
2	Liu et al. (2021)	+	
3	Szarpak et al.,all, (2021)	+	

+positive association

Lastly, the third subgroup included meta-analyses on the association of both the severity and risk of infection with the serum vitamin D level (n = 7) (Ghasemian et al. (2021); Pereira et al. (2020); Kazemi et al. (2021); Chiodini et al.; (2021), Kaya et al. (2021), Varikasuvu et al. (2022), Crafa et al. (2021))

Table 8: Association of SARS-CoV-2 severity in serum vitamin D deficiency/insufficiency and Risk of infection.

No	Studies	Severity		Mortality		ICU	Hospitalization	Infection	
1	**Ghasemian et al (2021)**	**+**		-		N/A	N/A	+	
2	Pereira et al. (2020)	+		+		N/A	+	±	
3	Kazemi et al. (2021)	+	+	− Crude	+ Adjusted	N/A	N/A	+ Crude	+ Adjusted
4	Chiodini et al. (2021)			+		+	+	+	
5	Kaya et al. (2021)	+		-		N/A	N/A	+	
6	Akbar et al. (2021)	+		+		N/A	N/A	+	
7	Varikasuvu et al. (2022)	+		-		N/A	N/A	+	
8	Grafa et al (2020)	+		-		N/A	N/A	+	

+positive association, -no significant association, ± moderate association.

All eight meta-analyses associated the low serum vitamin D levels with disease severity (Status vitamin D level with severity (n=7), mortality rates (n = 4), ICU rates (n = 1), hospitalization n = 2). The meta-analyses found that the level of vitamin D was lower in patients with severe disease, and patients with VDD had an increased risk of developing severe disease. (Table 6). The meta-regression analysis by Akbar et al. (2021) showed that the association between low serum 25 (OH) D and mortality was affected by male gender. It is important to note that the VDD had no significant effect on SARS-CoV-2 mortality in the five out of eight meta-analyses of this group in serum levels (Tables 6 & 8).This finding is noteworthy and confounding factors should be investigated for this association. Regrading to the risk infection of SARS-CoV-2 and VDD seven out of eight meta-analyses found that the infection rate increased in individuals with low serum Vitamin D levels. Only meta-analysis Pereira et al. (2021) did not find an association with a higher chance of SARS-CoV-2 infection. However, the results of the same meta-analysis shown that the serum vitamin D concentration was low in SARS-CoV-2 patients in relation to healthy individuals.

Overall 14 out of 15 meta-analyses found significant association with SARS-CoV-2 severity and VDD serum levels, only one study Halim et al. (2022) invested the association between TNF-α, IL-6, and Vitamin D Levels and SARS-CoV-2 Severity and Mortality and found a statistically insignificant difference of the mean vitamin D levels between patients with severe SARS-CoV-2 and non-severe SARS-CoV-2 and mortality.

Supplements

The second main group (table 9) was the vitamin D supplementation group (n = 8) Meta-analyses examined the association between disease severity and supplementation (Szarpak et al. (2021), Beran et al. (2022); Tentolouris et al. (2021); Rawat et al. (2021); Nikniaz et al. (2021); Shah et al. (2021); Hariyanto et al. (2021) Pal et al. (2021)).

Table 9: Association between vitamin D supplementation and risk of infection and/or severity of SARS-CoV-2 .

No	First Author	Severity	ICU	Mortality	Need for Invasive Ventilation
1	Szarpak et al.2021	N/A	+	+	N/A
2	Beran et al. (2022)	N/A	+	–	N/A
3	Tentolouris et al. (2021)	N/A	+	-	N/A
4	Rawat et al. (2021).	–	–	–	–
5	Niniaz et al. (2021)	N/A	N/A	+	N/A
6	Shah et al. (2021)	N/A	+	+	N/A
7	Hariyanto et al. (2021)	N/A	+	+	+
8	Pal et al. (2021)	+	+	+	N/A

+positive association, -no significant association ± moderate association.

The third group included meta-analyses that examined both the serum levels and supplements with the severity and the risk infection (table 10). (n=3) (Bassatne et al. (2021), Petrelli et al. (2021); Chen et al. (2021)). The meta-analyses in this group found conflicting results.

VDD correlation strongly with SARS-CoV-2 infection, severity, mortality Petrelli et al. (2021). Instead of any association between severity, ICU, need mechanical ventilation and riskinfection of SARS-CoV-2 (Chen et al.2021) and according with Bassaltne et al. (2021) thereis a positive trend between serum 25 (OH) D level <20 ng/ml and an increased risk of mortality, ICU admission, invasive ventilation or non-invasive ventilation and SARS-CoV-2 positivity. However, these associations were not statistically significant and the evidences are uncertain, supporting that there is a need more RCTs.

Table 10: Associations of both the vitamin D level and supplementation status with the risk of infection and severity of SARS-CoV-2.

No	First Author	Severity	ICU, Invasive Mechanical Ventilation Requirement	Mortality	Infection	Hospitalization
1	Bassatne et al. (2021)	± (uncertain évidence)	± (poor quality studies)	± (uncertain évidence)	± (uncertain évidence)	-
2	Petrelli et al. (2021)	+	N/A	+	+	N/A
3	Chen et al. (2021)	N/A	-	-	-	N/A

+positive association, -no significant association ± moderate association.

Additionally, 7 out of 8 meta-analyses established a strong association between vitamin D supplementation and disease severity (table 9-10). Pooled analyses of meta-analyses showed that the use of vitamin D supplements reduced ICU admission (n = 6) mortality (n = 6), mechanical ventilation (n = 1), and the hospitalization rate. Only one meta-analysis by Rawat et al. (2021) did not find any association with the severity SARS-CoV-2 (ICU admission, mortality rate, need of invasive ventilation).

Nevertheless, 4 out of 8 studies did not identify a significant association between vitamin D supplementation and SARS-CoV-2 induced mortality. The study by Beran et al. (2022) did not find an association between vitamin D and mortality. However, it was found that vitamin D supplementation was associated with a significant reduction in the intubation rate and a reduced hospitalization rate. In these studies, the supplemented and non-supplemented groups had the same levels of disease severity.

B.2.6 Reporting Biases

The majority of studies met the criteria and the standers of Preferred Reporting Items for Systematic reviews guidelines (PRISMA). The inclusion or exclusion of studies in a systematic review for all included studies was clearly defined prior of all studies using more than 4 databases at the minimum and the search strategy included both MESH terms and text words. However, some studies using language restriction. All studies present the results with traditionally displayed forest plot, except one study (Szarpak et al., 2021) presented it in the table.

The overall publication bias in this review it appears to be low. However, some meta-analyses there are no information available concerning the publication bias, mainly because of the small number of includes studies was less ten. Additional some outcomes of individual meta-analyses had a high publication bias, hence had a minimal effect on the overall comprehensive effect estimation. This review can, be identified to have a high heterogeneity. Most of the meta-analyses reviewed were high or moderate heterogeneous in their outcomes. This heterogeneity could downgrade the certainty of this review. Factors, such as publication bias, risk of bias, imprecision, indirectness, and inconsistency affect the certainty of evidence. The number of studies and the type of studies included in the individual meta-analyses influenced the certainty of evidence. For instance, the certainty of the evidence was moderate to high in RCTs, however, it remained low in observational studies. Based on the assessment of the heterogeneity, risk of bias and publication bias, the certainty of this review can be classified as moderate.

B.3 Discussion

In this systematic review, we analyzed 29 meta-analyses who analyzed the association between vitamin D and SARS-CoV-2 severity, and risk of infection.

The meta-analyses showed that high serum vitamin D levels reduce the risk of SARS-COV-2 infection (Teshome et al. 2021, Liu et al. 2021, Szarpak 2021, Ghasemian et al. 2021,Kazemi et al. 2021, Chiodini et al. 2021, Kay et al.202, Akbart et al.2021, Varikasuvu et al.2022, Grafa et al.2021, Bassante et al. 2021 Petrelli et al. 2021) and limit disease severity, including the need for hospitalization (Pereira et al.2021; Chiodini et al.2021), mortality (Ben-Eltriki et al.2021, AI Kiyumi et al.2021, Wang et al. 2021, Oscanoa et al. 2021, Pereira et al.2021, Chiodini et al.2021, Akbar et al.,2021, Varikasuvu et al.2022, Grafa et al.,2021, Bassatne et al. 2021, Petrali et al.2021), ICU admission (Ben-Eltriki et al. 2021, Chiodini et al.2021, Bassatne et al. 2021), and invasive ventilation (Ben-Eltriki et al. (2021), Bassatne et al. 2021).

Vitamin D supplementation was also associated with a reduced SARS-CoV-2 infection rate (Bassante et al. 2021, Petrelli et al. 2021) and a reduced level of disease severity, including reductions in hospitalization (Szarpak et al. 2021, Beran et al. 2021), mortality (Szarpak et al.

2021, Tentolouris et al. 2021, Niniaz et l., 2021, Shah et al. 2021) Pereira et al. 2020, Kazemi et al. (2021), Chiodini et al. (2021), Hariyanto et al. 2021,Pal et al. 2021), ICU admission (Szarpak et al. 2021, Beran et al. 2021, Tentolouris et al. 2021, Shah et al. 2021, Hariyanto et al. 2021, Pal et al. 2021,Bassatne et al. 2021), and invasive ventilation (Szarpak et al.2021, Hariyanto et al.2021, Bassante et al. 2021, Petlalli et al.2021). These findings can be explained by various mechanisms. Firstly, vitamin D upregulates ACE2 gene expression, leading to decreases in the inflammatory response and risk of infection (Tomaszewska et al., 2022). Other mechanisms of vitamin D actions include the direct inhibition of virus replication and modulation of the immune system. (De Smet et al. 2020). Other mechanisms of vitamin D actions include the direct inhibition of virus replication and modulation of the immune system. (De Smet et al. 2020). Specifically Vitamin D inhibits the development of pro-inflammatory Th-17 cells in addition to modulating pro-inflammatory cytokines like IL-1, IL-6, and IL-10, which are heavily involved in the cytokine storm, and they cause the SARS-CoV-2 mortality.

The mechanisms through which vitamin D might affect SARS-CoV-2 severity and the risk of infection are unclear. The evidence indicates that vitamin D might help in the treatment of SARS-CoV-2 by preventing the cytokine storm a (dysregulated immune response) and subsequent ARDS, which is commonly the cause of mortality.

Not all meta-analyses have reported a strong association between the Vitamin D level, deficiency and supplementation with the SARS-CoV-2 risk and disease severity. A significant correlation has been found between the Vitamin D level and the SARS-CoV-2 risk and disease harshness. For instance, a meta-analysis examined the associations between tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and vitamin D with the severity and mortality of SARS-CoV-2 without definitive results (Halin and al., 2022). Two studies by (Chen et al., 2021), and (Rawat et al., 2021) did not establish an association between vitamin D supplementation and disease severity, risk infection, or mortality. Again, we should take into account two shortcomings in the meta-analyses of (Chen et al., 2021) the level of heterogeneity was high for supplementation (I^2 = 64%, ICU admissions (I^2 = 90%), a significantly decreased risk of SARS-CoV-2 infection (I^2 = 79%), and the number of studies (n = 536,105 patients, 13 studies). This indicates that there are still missing elements, and with such a small sample of studies, we cannot draw reliable conclusions. Likewise, in the Meta-analysis by (Rawat et al., 2021), the publication bias was not assessed because of the limited number of studies (n < 10). According to the GRADE, the certainty of the evidence for mortality, ICU admission, and mechanical ventilation was ``very low`, which means that any estimation of effects is extremely uncertain.

Regarding the mortality from SARS-CoV-2, even though many studies have shown a significant association between VDD and SARS-CoV-2 mortality (Abrishami et al. 2020, Radujkovic et al. 2020, Angelidi et al. 2021, Campi et al. 2021, De Smet, De Smet et al. 2021, Infante et al. 2021, Karahan and Katkat 2021) and there is evidence that vitamin D can help to treat SARS-CoV-2 by preventing the cytokine storm and subsequent ARDS, which are common causes of death, is noteworthy that four meta-analyses found a positive correlation between disease severity and serum vitamin D insufficiency however not with mortality (Ghasemian et al. 2021, Kazemi et al. 2021, Kaya et al. 2021, Grafa et al. 2021). Then Halim et al.2022 found that VDD insignificantly increased the risk of mortally of SARS-CoV-2. Similarly, Tentolouris et al. (2021) found an association with ICU addition of SARS-CoV-2 and VDD but did not found significant association with mortality. The meta-analysis by Beran

et al. (2021) found that vitamin D deficiency/inefficiency was associated with a lower intubation rate and shorter length of hospital stay, but it did not found significant association with mortality. Finally Rawat et al. (2021) and Chen et al. (2021) did not find any correlation with SARS-CoV-2 and VDD/VDI in their several outcomes including the mortality. Overall, nine meta-analyses in this systematic review showed that vitamin D deficiency/insufficiency is not associated with SARS-CoV-2 mortality. This may be due to confounding factors, because the mechanism of vitamin D as mentioned above, very well explains the significant association between VDD and COVID 19 mortality. Furthermore, to be taken into account here, the meta-analysis reviewer by Halim et al. (2020) that found the TNF-α is insignificantlyassociated with SARS-CoV-2 severity, however significantly associated with SARS-CoV-2 mortality supporting the results of remaining 15 meta-analyses (n=15). Therefore, more investigations are required to support the conflicting results in these 9 studies. This was not observed for the other our outcomes.

Another aspect to note is the vitamin D dosage for administration of supplements. Only two meta-analysis investigated this aspect. (Martineau et al., 2017). Tentolouris et al. (2021) found that high vitamin D doses did not significantly reduce mortality OR=1.444; (95% CI: 0.705–2.959, $p = 0.316$) or ICU admission rates OR=0.603; (95% CI: 0.348–1.045, $p = 0.072$) "but low doses" significantly minimized the rates of mortality and ICU admission in SARS-CoV-2 patients. Similar results were also found meta-analysis by Akbar et al. (2021) that showed vitamin D3 benefits were observed with a dose of <800 international units (IU), while a statistically non-significant trend was found with 800–2000 IU, and no benefit was found with ≥2000 IU (Akbar et al. 2021).

These results are supported by another analysis that indicated that Vitamin D supplementation is linked to a lower rate of acute respiratory tract infections (Martineau, 2017). Moreover, seven studies identified a significant link between vitamin D supplementation and viral respiratory tract infections RR=0.89, (95% CI: 0.79–0.99, $I^2 = 20.7\%$, $p = 0.272$), thus concluding that vitamin D can protect adults in the USA and Canada. On the other hand, according to the findings from a recent meta-analysis of clinical trials, RCTs, controlled clinical trials, and quasi-RCTs, (Vlieg- Boerstra et al., 2022) reported that six studies did not find a notable relationship between Vitamin D supplementation and viral respiratory tract infections RR=0.88,(95% CI:0.66–1.11, $I^2 = 80.4\%$, $p = 0.000$). Similar recent meta-analysis of RCTS (Cho et al. 2022) found that vitamin D supplementation has no clinical effect in the prevention of Acute Respiratory.

In summary, the majority of 29 meta-analyses found a positive association between supplements and risk of severity and risk of infection. However, more evidence required to bring a light on this aspect. Vitamin D was not associated with adverse events in any meta-analyses reviewed, indicating its safety the sampled studies depict variations in vitamin D dosage administration, ranging from low daily doses, like 1000 IU of cholecalciferol to high-dose boluses, like 400,000 IU of cholecalciferol. The appropriate dosage that will benefit the patient in the case of supplements and which groups of patients supplementation mainly benefits are unknown.

The results of this systematic review are important for users such as health professionals and policymakers. SARS-CoV-2 created an opportunity to explore the best interventions for viral diseases, most of which lack treatments. Increased vitamin D intake or adequate exposure to

sunlight can be considered as a preventive measure for reducing the risk of SARS-COV-2. Nonetheless, more evidence should be collected from clinical trials to establish the effectiveness and safety of vitamin D as a treatment for SARS-COV-2 in specific populations. For example, information on the ideal dose and risk factors focused on patients with diabetes or diabetic retinopathy and postmenopausal women or in terms of the rate of metabolism, age, obesity, comorbidities, nutritional habits, and geographical region should be examined. An upcoming systematic review of meta-analyses will examine the use of Oral high-dose vitamin D for the treatment of diabetic patients with SARS-CoV-2 (Nie et al., 2021) Evidence from ongoing trials, such as CORONAVIT, COVITD-19, COVIDIOL, VIVID, and COVIT-TRIAL, will determine with greater precision the association of vitamin D with SARS-CoV-2.

Limitations of Evidence

Three main limitations affect the quality of evidence presented. First, there was a high level of heterogeneity in the majority of studies. As SARS-CoV-2 is a new infection, there is a lack of adequate evidence to permit the application of stricter exclusion criteria in the study designs. A design including only RCTs would have minimized the heterogeneity in this review. On the other hand, including all available meta-analyses provided a comprehensive synthesis of the data on this topic.

Secondly, as we analyzed data in after level from tertiary sources it also affects our own results, one example is the failure of some meta-analyses to establish the publication risk of bias due to confounding variables. Furthermore, a significant gap exists in the literature in terms of identifying the qualitative synthesis of available evidence. The characteristics of individuals with stronger protective effects and the types of intervention (e.g., dose, regimen, duration) that yield the greatest benefits remain unclear. The majority of meta-analyses have failed to identify vitamin D dosage strategies for use in SARS-CoV-2 detection methods and how often to apply them. Moreover, less than half of the meta-analyses that the studies' results were not dissected based on the sex or geographical location, or the BMI of the participants. This issue may be deleterious to the authenticity of the findings, as body composition and body fat content are dissimilar between males and females and may affect vitamin D levels and SARS-CoV-2 severity.

Another limitation is the absence of GRADE-qualified evidence. Considering that this is a systematic review, it was not possible to assess the degree of bias in individual meta-analyses, since they did not include GRADE qualified evidence themselves. Only four out of twenty-nine meta-analyses provided a GRADE appraisal. The data comes from tertiary sources that become more prone to high risk of bias.

However, this is the first systematic review of meta-analyses reporting on the up-to-date link between vitamin D status and SARS-CoV-2 severity and infection. All eligible meta-analyses were reviewed carefully for their quality and met the standards by PRISMA. The available data is still limited and the aforementioned limitations are due to this reason.

Conclusion

Vitamin D deficiency/insufficiency seems to be associated with increased disease severity and risk of infection related to SARS-CoV-2 infection. SARS-CoV-2 positive patients with the lowest levels of vitamin D have higher incidences of hospitalization, disease severity, and ICU admission. Again, vitamin D supplementation was found to be effective for curbing SARS-CoV-2.Patients treated with vitamin D had lower risks of hospitalization, ICU admission, and disease severity.Future researchers should explore the appropriate vitamin D dosage supplements necessary for the management of SARS-CoV-2 and other ailments. More evidence should be collected through clinical trials to establish the effectiveness and safety of vitamin D in treating SARS-CoV-2.

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Appendix 1: PRISMA checklist 2020 - Preferred Reporting Items for Systematic Reviews.

Section and Topic	Item #	Checklist Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	0
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	13
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	14
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify thedate when each source was last searched or consulted.	15
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	15
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each recordand each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	16
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in theprocess.	16
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in eachstudy were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	17
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	N/A
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	17
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	18

Section and Topic	Item #	Checklist Item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics andcomparing against the planned groups for each synthesis (item #5)).	19
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	19
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe themodel(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	19
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included inthe review, ideally using a flow diagram.	19
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	20
Study characteristics	17	Cite each included study and present its characteristics.	20
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	21-27
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision(e.g. confidence/credible interval), ideally using structured tab. or plots.	27
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	27-32
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g.,confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe	32-55

Section and Topic	Item #	Checklist Item	Location where item is reported
		the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	32-55
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	32-55
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	32-55
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	44
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	60
	23b	Discuss any limitations of the evidence included in the review.	63
	23c	Discuss any limitations of the review processes used.	63
	23d	Discuss implications of the results for practice, policy, and future research.	63
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from includedstudies; data used for all analyses; analytic code; any other materials used in the review.	

Appendix 2: List of Eligible and Excluded Meta-analyses.

2a: List of Eligible Meta-Analyses

	First Author	Study Title	Web link
1	Munshi et al.(2021)	Vitamin D insufficiency as a potential culprit in critical SARS-COV-2 patients.	https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.26360
2	Ben-Eltriki et al.(2021)	Association between Vitamin D Status and Risk of Developing Severe SARS-COV-2 Infection: A Meta-Analysis of Observational Studies	**https://pubmed.ncbi.nlm.nih.gov/34464543/**
3	Al Kiyumi et al. (2021)	The Impact of VDDon the Severity of Symptoms and Mortality Rate among Adult Patients with SARS-CoV-2 : A Systematic Review and Meta-Analysis	**https://www.embase.com/search/results?subaction=viewrecord&rid=14&page=2&id=L636815408** **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8793953/**
4	Wang et al. (2021)	Association of VDDwith SARS-COV-2 infection severity: Systematic review and meta-analysis	**https://pubmed.ncbi.nlm.nih.gov/34160843/**
5	Halim et al. (2022)	The Association between TNF-α, IL-6, and Vitamin D Levels and SARS-CoV-2 Severity and Mortality: A Systematic Review and Meta-Analysis.	**https://www.mdpi.com/2076-0817/11/2/195/htm**
6	Oscanoa et al. (2021)	The relationship between the severity and mortality of SARS-CoV-2 infection and 25-hydroxyvitamin D concentration — a meta-analysis.	**https://journals.viamedica.pl/advances_in_respiratory_medicine/article/view/72317**
7	Teshome et al. (2021	The Impact of Vitamin D Level on SARS-CoV-2 Infection: Systematic Review and Meta-Analysis)	**https://www.frontiersin.org/articles/10.3389/fpubh.2021.624559/full**
8	Liu et al (2021)	Low vitamin D status is associated with coronavirus disease 2019 outcomes: a systematic review and meta-analysis	https://www.embase.com/search/results?subaction=viewrecord&rid=5&page=3&id=L2010726620 **https://www.ijidonline.com/article/S1201-9712(20)32600-X/fulltext**
9	Szarpak et al.2021)	A systematic review and meta-analysis of effect of vitamin D levels on the incidence of SARS-COV-2	**https://journals.viamedica.pl/cardiology_journal/article/view/83912**
10	Ghasemian et al. (2021)	The role of vitamin D in the age of SARS-CoV-2: A systematic review and meta-analysis.	**https://onlinelibrary.wiley.com/doi/10.1111/ijcp.14675**
11	Pereira et al. (2020)	VDDaggravates SARS-CoV-2 : systematic review and meta-analysis	
12	kazemi et al. (2021)	Association of Vitamin D Status with SARS-CoV-2 Infection or SARS-CoV-2 Severity: A Systematic Review and Meta-analysis	
13	Chiodini et al. (2021)	Vitamin D Status and SARS-CoV-2 Infection and SARS-CoV-2 Clinical Outcomes.	
14	Kaya et al.2021)	The role of VDDon SARS-COV-2 : a systematic review and meta-analysis of observational studies	

https://www.tandfonline.com/doi/full/10.1080/10408398.2020.184 1090

https://www.embase.com/search/results?subaction=viewrecord &rid=25&page=1&id=L634636464
https://pubmed.ncbi.nlm.nih.gov/33751020/

https://pubmed.ncbi.nlm.nih.gov/35004568/

https://pubmed.ncbi.nlm.nih.gov/34607398/

	First Author	Study Title	Web link
15	Akbar et al. (2021)	Low Serum 25-hydroxyvitamin D (Vitamin D) Level Is Associated With Susceptibility to SARS-COV-2 , Severity, and Mortality: A Systematic Review and Meta-Analysis	**https://www.frontiersin.org/articles/10.3389/fnut.2021.660420/full**
16	Varikasuvu et al. (2022)	SARS-COV-2 and vitamin D (Co-VIVID study): a systematic review and meta-analysis of randomized controlled trials.	**https://pubmed.ncbi.nlm.nih.gov/35086394/**
17	Grafa et al. (2021)	Influence of 25-hydroxy-cholecalciferol levels on SARS-CoV-2 infection and SARS-COV-2 severity: A systematic review and meta-analysis.	**https://www.embase.com/search/results?subaction=viewrecord&rid=11&page=2&id=L2013112112 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8215557/**
18	Szarpak et al. (2021)	Vitamin D supplementation to treat SARS-CoV-2 positive patients. Evidence from meta-analysis	**https://pubmed.ncbi.nlm.nih.gov/34642923/**
19	Beran et al. (2022)	Clinical significance of micronutrient supplements in patients with coronavirus disease 2019: A comprehensive systematic review and meta-analysis	**https://clinicalnutritionespen.com/article/S2405-4577(22)00002-X/pdf**
20	Tentolouris et al. (2021)	The effect of vitamin D supplementation on mortality and intensive care unit admission of SARS-COV-2 patients. A systematic review, meta-analysis and meta-regression.	**https://pubmed.ncbi.nlm.nih.gov/34965318/**
21	Rawat et al. (2021)	Vitamin D supplementation and SARS-COV-2 treatment: A systematic review and meta-analysis	**https://www.embase.com/search/results?subaction=viewrecord&rid=12&page=2&id=L2013324081 https://www.sciencedirect.com/science/article/pii/S1871402121002095?via%3Dihub**
22	Nikniaz et al. (2021	The impact of vitamin D supplementation on mortality rate and clinical outcomes of SARS-COV-2 patients: A systematic review and meta-analysis)	**https://www.medrxiv.org/content/10.1101/2021.01.04.21249219v1**
23	Shah et al. (2021)	Vitamin D supplementation, SARS-COV-2 and disease severity: a meta-analysis.	**https://academic.oup.com/qjmed/article/114/3/175/6118232?login=false**
24	Hariyanto et al. (2021)	Vitamin D supplementation and Covid-19 outcomes: A systematic review, meta-analysis and meta-regression	**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8420388/**
25	Pal et al. (2021)	Vitamin D supplementation and clinical outcomes in SARS-COV-2 : a systematic review and meta-analysis	**https://pubmed.ncbi.nlm.nih.gov/34165766/**
26	Bassatne et al. (2021)	The link between SARS-COV-2 and VItamin D (VIVID): A systematic review and meta-analysis	**https://www.metabolismjournal.com/article/S0026-0495(21)00053-6/fulltext**
27	Petreli et al. (2020)	Therapeutic and prognostic role of vitamin D for SARS-COV-2 infection: A systematic review and meta-analysis of 43 observational studies	**https://www.embase.com/search/results?subaction=viewrecord&rid=9&page=2&id=L2011577033 https://www.sciencedirect.com/science/article/pii/S0960076021000765?via%3Dihub**
28	Ebrahimzadeh et al. (2021)	Association between vitamin D status and risk of SARS-CoV-2 in-hospital mortality: A systematic review and meta-analysis of observational studies	**https://www.embase.com/search/results?subaction=viewrecord&rid=5&page=1&id=L636865339 https://pubmed.ncbi.nlm.nih.gov/34882024/**
	Chen et al. (2021)	Low vitamin D levels do not aggravate SARS-COV-2 risk or death, and vitamin D supplementation does not improve	29 outcomes in hospitalized patients withSARS-COV-2 : a meta-analysis and

GRADE assessment of cohort studies and RCTs.

https://nutritionj.biomedcentral.com/articles/10.1186/s12937-021-00744-y

2b: List of Excluded Meta-Analyses

Reason for exclusion	Study Title	Web link
Nutriment supplements associated with Severe acute respiratory disease, but this was conducted in 2019 so was done without a population with SARS-COV-2	Nutrient supplementation for prevention of viral respiratory tract infections in healthy subjects: A systematic review and meta-analysis	https://www.embase.com/search/results?subaction=viewrecord&rid=20&page=1&id=L636590262 https://www.embase.com/search/results?subaction=viewrecord&rid=21&page=1&id=L636378030 https://onlinelibrary.wiley.com/doi/full/10.1111/all.15136
Not an original meta-analysis, just evidence from meta-analyses	The Role of Vitamin D in The Age of SARS-COV-2 : A Systematic Review and Meta-Analysis Along with an Ecological Approach	https: https://www.medrxiv.org/content/10.1101/2020.06.05.20123554v2//www.embase.com/search/results?subaction=viewrecord&rid=23&page=1&id=L2014097417
Acute respiratory infections: but Without patients SARS-COV-2	1. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials 2. Risk of respiratory infections Effect of micronutrient supplements on influenza and other respiratory tract infections among adults: a systematic review and meta-analysis	https://pubmed.ncbi.nlm.nih.gov/33798465/ https://scholar.harvard.edu/files/sabri/files/abioye_2021_-_effect_of_micronutrient_supplements_on_influenza_and_other_respiratory_tract_infections_among_adults_-_a_systematic_review_and_meta-analysis.pdf
Not an original meta-analysis, just evidence from meta-analyses	SARS-COV-2 Mortality Risk Correlates Inversely with Vitamin D3 Status, and a Mortality Rate Close to Zero Could Theoretically Be Achieved at 50 ng/mL 25(OH)D3: Results of a Systematic Review and Meta-Analysis (Borche et al 2021)	https://www.mdpi.com/2072-6643/13/10/3596/htm
Others study design	Optimum Solar Radiation Exposure or Supplemented Vitamin D Intake Reduce the Severity of SARS-COV-2 Symptoms?	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7829816/

Reason for exclusion	Study Title	Web link
Ongoing study protocols	-Vitamin C and D supplementation and the severity of SARS-COV-2 : A protocol for systematic review and meta-analysis, -Oral high dose vitamin D for the treatment of diabetic patients with SARS-COV-2 : A protocol for systematic review and meta-analysis	https://www.embase.com/search/results?subaction=viewrecord&rid=3&page=3&id=L634466138