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COVID-19 and Vitamin D: Is There a Direct Relationship Between Vitamin D Deficiency and COVID-19 Severity?

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Abstract: Objectives: ***This study investigates whether there is a credible link between Vitamin D concentration in the human blood and COVID-19 infection, severity, and death in the general population.***
Design: ***The study adopts a meta-analytical approach to synthesize available secondary information. Emphasis is given to works published within the COVID-19 duration. The study draws articles from scholarly medical sites to provide credit to the analysis and results.***
Setting: ***The study is set on a global stage because the articles are drawn from different parts of the world. Mainly, the changing nature of the virus and the continuing revelation of its operations under various conditions arouse interest among scholars that share investigation procedures.***
Selection, Entry, Exclusion Criteria Interventions: ***The articles used in the investigation are those from peer reviews. Mainly, articles with a document identifier number (DOI) qualified for the analysis. At the same time, the study focused on articles exploring the relationship between COVID-19 and Vitamin D only.***
Primary and Secondary Outcome Measures: ***The primary outcome is that Vitamin D improves the body's immune response and suppresses viral activity. The secondary effect is that Vitamin D deficiency, coupled with other comorbidities, increases the risk of death and severe coronavirus infection.***
Results: ***Results confirm a strong relationship between 25(OH)D concentration and the body's ability to fight the COVID-19 infection. Individuals with low Vitamin D concentrations of less than 20 ng/ml experienced severe symptoms. Findings indicate that Vitamin D3 supplements increase 25(OH)D levels, making the body withstanding the virus.***
Conclusion: ***Thus, Vitamin D concentration in the blood directly correlates with COVID-19 severity and mortality.***
Keywords: COVID-19, Vitamin D, Immune System, SARS, ARDS

I. STRENGTHS AND LIMITATIONS OF THIS STUDY

The strength of this study includes:

- ✓ Exclusive reliance on the latest studies published between 2020 and 2021
- ✓ Focusing on peer-reviewed works that give credibility to the analysis
- ✓ Drawing results from multiple international scientific studies

The weaknesses of the study are:

- ❖ Inadequate number of cohort studies since COVID-19 is a relatively new virus that continues to mutate
- ❖ Focuses on secondary data without any primary information from qualified and experienced individuals in the field

II. STUDY BACKGROUND

A. COVID-19

Coronavirus disease is an ailment ravaging the world with multiple variant strains. The World Health Organization (WHO) renamed the 2019 nCoV to COVID-19, a disease characterized by pneumonia symptoms. It is thought the disease originated in Wuhan City in China (Shakoor et al., 2021). The airborne virus rapidly spread from its origin to other parts of the globe in record time due to the increased movement of people through road, rail, and air transport. According to Kumar et al. (2021), COVID-19 is characterized by lower respiratory tract viral infection with symptoms including oxidative stress that make it harder for patients to absorb an adequate amount of oxygen into the bloodstream (Slominski et al., 2021). Figure 1 is a diagrammatic representation of the COVID-19 virus structure. The spike glycoprotein attaches to healthy cells, enter, multiply, and burst open to release the newly-created viruses.

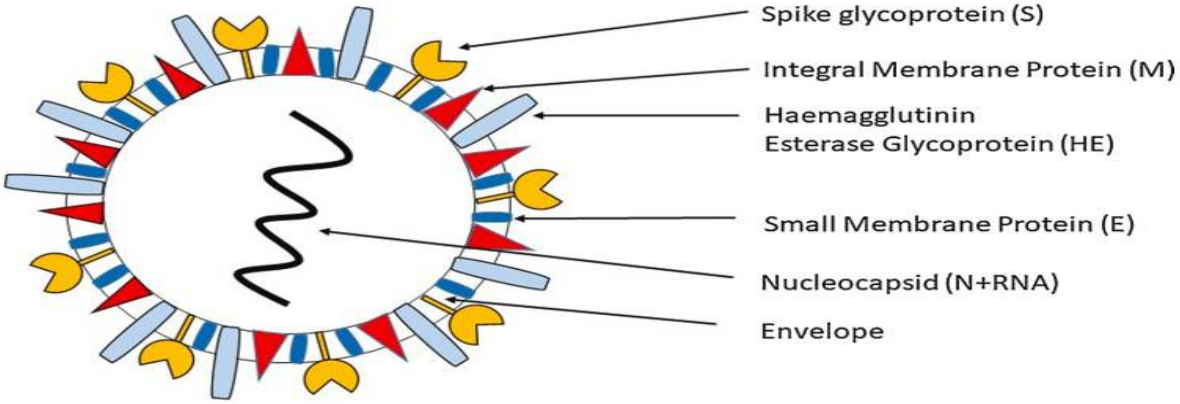

Fig. 1. Diagrammatic representation of SARS-CoV-2 coronavirus virion.

Fig. 1 – Diagrammatic Representation of the SARS CoV-2 Coronavirus Variant
(**Source:** Kumar et al., 2021, p. 2)

Slominski et al. (2021) define COVID-19 as a severe respiratory syndrome containing a positive RNA strain belonging to the *Coroniridae* family. The virus has a moderately low mortality rate, albeit several times more lethal than conventional influenza viral infections (Slominski et al., 2021). Mansur et al. (2020) add that the COVID-19 virus "binds to ACE2 enzyme, making more angiotensin II available to cause damage" (p. 268). Thus, increased production of angiotensin II in the body fosters an attack on the respiratory system and makes the ailment more potent among infected patients.

B. Vitamin D

Vitamin D is one of the most valuable nutrients in the body and can be found on many food items and the sun's ultraviolet rays. Iddir et al. (2020) clarify that Vitamin D is present in eggs, mushrooms, fish, and fortified milk diets. However, the higher amount of functional Vitamin D comes from the sun's rays. In particular, the ultraviolet-B (UVB) is absorbed through the human skin and is responsible for reducing cytokine storms (Grant et al., 2020). Slominski et al. (2021) describe Vitamin D as a fat-soluble prohormone that plays an essential role in physiological functions in the body, such as the regulation of adaptive and innate immunity in the body. Therefore, Vitamin D is vital to fighting pathogens in the body. From this information, this study will investigate whether there is a credible relationship between Vitamin D in the body and the severity of COVID-19 among patients.

III. METHODOLOGY

A. Population

The study focuses on secondary information draw from international publications. Some studies explore the relationship between COVID-19 and Vitamin D in Poland, the US, and the UK (Grant et al., 2020). Another touches on Switzerland, Italy, Korea, Russia, Mexico, Austria, and Germany (Mercola et al., 2020). The study design allows information from diverse populations to be combined to identify the correlation between studied results.

B. Study Design

A meta-analysis study approach is preferred because it helps gather data and information from multiple sources and compare the outcomes to identify trends for generalization purposes.

C. Study Setting

The study is set on the global stage. The data used in the study comes from secondary research activities conducted in different parts of the world, bringing together related information regarding COVID-19 and Vitamin D, which helps establish points of convergence and divergence in the results. It also helps identify flaws in study designs and possible conflicts in data interpretation. Moreover, COVID-19 is a mutating virus and currently spreading in all parts of the globe. Hence, setting the study on a global stage fosters accumulating information and data from multiple sources.

D. Inclusion/ Exclusion Criteria

The study only includes peer-reviewed literature for data analysis. However, only publications focusing on the relationship between COVI-19 and Vitamin D qualify for the meta-analysis. Some of the publications explore the risk of COVID-19 infection and the amount of Vitamin D in the body (Mercola et al., 2020). Other studies examine the effect of Vitamin D deficiency on COVID-19 patient outcomes (Radujkovic et al., 2020). Moreover, some studies focus on the application of Vitamin D, specifically Vitamin D3 (cholecalciferol), for COVID-19 patient management (Kumar et al., 2021; Slominski et al., 2021; Grant et al., 2020). In addition, both qualitative and quantitative studies that qualify in the previously mentioned criteria are included in the study.

IV. LITERATURE REVIEW

Vitamin D is strongly associated with a more robust immune system in the human body. Slominski et al. (2020) argue that Vitamin D activation follows both canonical and non-canonical routes. In canonical pathways, the liver, using CYP2R1 and CYP27A1, metabolize Vitamin D3 (Slominski et al., 2020). The kidney utilizes CYP27B1 to metabolize 1,25-dihydroxyvitamin D3. Moreover, Vitamin D metabolism also occurs in other organs, including the immune system and the skin (Slominski et al., 2020). Xu et al. (2020) maintain that Vitamin D acts as a potent immunosuppressant by inhibiting cytokine release that fortifies the COVID-19 virus. Vitamin D deters inflammation and stimulates neurotrophins production, especially the Nerve Growth Factor (NGF) (Xu et a., 2020). Bergman (2020) contends that Vitamin D receptors (VDR) activate between 200 and 500 genes associated with the body's defense mechanism. Therefore, Vitamin D is strongly associated with a more robust immune system.

Vitamin D activates systems that help fight the COVID-19 virus. Mansur et al. (2020) state that Vitamin D stimulates the renin-angiotensin-aldosterone system (RAAS) that the coronavirus inhibits, exacerbating the infection rate. Conventionally, the COVID-19 virus binds itself to the ACE2 enzyme, increasing the production of angiotensin II responsible for system-wide destruction (Mansur et al., 2020). The introduction of Vitamin D in the body leads to the inhibition of RAAS mediators in body cells, thereby inhibiting ACE activities and lowers angiotensin II levels (Mansur et al., 2020). The challenge is that Vitamin D deficiency leads to an upsurge in COVID-19 bonding and angiotensin II production (Shakoor et al., 2021), resulting in rapid and often irreversible organ damage that leads to the demise of an infected person.

V. DATA

The first article selected for this analysis is by Xu et al. Xu et al.'s (2020) work qualifies for this meta-analytical investigation because it premises the possibility of administering Vitamin D for COVID-19 management. The study analyzes ongoing clinical trials for the SARS virus categories, with four of the trials focusing on COVID-19 and taking place between 2020 and 2021. Another five clinical trials focus on respiratory infections, three on autoimmune diseases, and three on neurological disorders. All these conditions rely on a robust immune system to contain and control infections. The article further illustrates Vitamin D's treatment pathways in managing human diseases. Xu et al.'s report is credible because all authors are from the Division of Hematology and Oncology in Loma Linda University, California, USA. The article also relies on credible sources with 98 peer-reviewed, one scholarly book, and four credible websites offering health information. The report also explains the ratio and proportion of Vitamin D application under different circumstances.

Moreover, integrating summary tables and figures makes it easier to detect the relationship between Vitamin D adequacy in the body and COVID-19 severity. Furthermore, the data presentation links Vitamin D action on other viruses, including HIV, EBV, H1N1, HCV, Rota, and Dengue viral infections (Xu et al., 2020). Hence, the report confirms a relationship between Vitamin D and COVID-19 severity.

Slominski et al.'s article offers a descriptive approach to COVID-19's operations and the effect of Vitamin D deficiency. Slominski et al. (2021) hypothesize that the Vitamin D delivery route affects the overall patient outcome. The study demonstrated that humans produce $20,23(OH)_2D_3$ and $20(OH)D_3$ hydroxyderivatives. The study shows the effect of cytokine storm production triggered by viral overload, with interferons, colony-stimulating factors, interleukins 1, 6, and 17, chemokines causing organ damage, and hyperinflammation (Slominski et al., 2021). The study has validity with the authors from a medical research background in Boston University, University of Alabama, and Research Triangle Park. Likewise, the study identifies each system, interaction, and Vitamin D form by its chemical formula and utilizes a language befitting scholar in the field.

Moreover, the article relies exclusively on 71 peer-reviewed journals in the medical field, reinforcing the study's authority. Although the survey successfully explains Vitamin D's action in suppressing the COVID-19 virus, placing the associated table and figures in the appendices makes it cumbersome to refer to them while reading the prose. Nevertheless, the chemical interactions presented in the images enhance an understanding of system operation.

Bergman's article explores the Vitamin D effect in the body when applied in different quantities. The study indicates that a Vitamin D dosage of between 1000 and 2000 IU a day is non-toxic and adequate in sustaining a healthy body (Bergman, 2020). However, the study found a link between UV exposure level and COVID-19 mortality (Bergman, 2020). Bergman comes from a medical background because he serves in the Department of Laboratory Medicine at Karolinska Institute in Sweden. However, the quality of data used in the presentation is average, given that there are no diagrammatic or empirical data supporting the assertion. The article is also tiny and relies on a small number of reports to support opinions.

Nonetheless, Bergman's work proves credible because the 13 references used are all peer-reviewed. It would have been vital to supporting some assertions with the requisite information, especially on the safety of administering 10,000 IU daily. Furthermore, reliance on a small sample size might have led to the conclusion that low Vitamin D levels increase the risk of COVID-19 infections.

The results also appear to conflict with findings because the author found a link between the administration of Vitamin D supplements among patients with Parkinson's disease and the likelihood of COVID-19 infection. Thus, Bergman's article projects information that conflicts needing further exploration.

Kumar et al.'s article is definite on the putative role of Vitamin D and how such action enhances COVID-19 management. The study explores the pathophysiological processes associated with SARS-CoV-2 (COVID-19), noting the elevated IL-2, MCP1, IL-10, IL-7, IP-10, TNF, and G-CSF among infected patients. Furthermore, the study explores the interaction between Vitamin D and virus suppression.

The diagrammatic representation of the two types of interactions confirms the usefulness of Vitamin D in boosting the body's immune response against the virus. However, the authors quickly point out that Vitamin D works well when combined with other medications, especially dexamethasone, reducing the mortality rate. Likewise, an independent trial involving 277 COVID-19 patients led to early removal from ventilation support and lowered the overall mortality rate. The study's reliance on a colossal number of peer-reviewed studies, coupled with collaboration with medical professionals in various institutes in India and the United States, gives credibility to the study.

Additionally, the combination of colored figures in the report makes it easier to follow the interaction between chemicals in the body and the virus. The study confirmed past works by undertaking independent research on the effectiveness of Vitamin D and dexamethasone in COVID-19 management.

Mansur et al.'s article also offers an analysis of Vitamin D's function in COVID-19 management. Mansur et al. (2020) confirm that Vitamin D is instrumental in activating innate and adaptive immunity. The authors are members of recognized medical institutions in Argentina.

The authors rely on peer-reviewed articles only to support their findings. Furthermore, their results also introduce other associated risk factors that exacerbate COVID-19 severity, including age, hypertension, diabetes, and chronic respiratory and kidney diseases (Mansur et al., 2020).

Nevertheless, results confirm that Vitamin D boosts the body's immune system by activating anti-inflammatory cytokines, antifibrotic reaction, vasodilation, and non-hypoxic condition (Mansur et al., 2020). The study succeeds in demonstrating the effects of different Vitamin D concentrations on body function. Thus, the study succeeds in highlighting the importance of Vitamin D on COVID-19 management.

Shakoor et al.'s article investigates COVID-19's dysregulation of the human immune system and the use of Vitamin D in suppressing its activity.

The study draws information from credible sources, including PubMed, Google Scholar, and Science Direct to collect high-quality scholarly studies to support their hypothesis (Shakoor et al., 2020). A combination of tables and colored diagrams with chemical interactions help reinforce Vitamin D interaction and its immunomodulatory function, as shown in Figure 2 below. The study also demonstrates the interaction between Vitamin D absorption and zinc. Thus, the study's integration of scholarly works confirms that Vitamin D is a rich source and immune activator in the body.

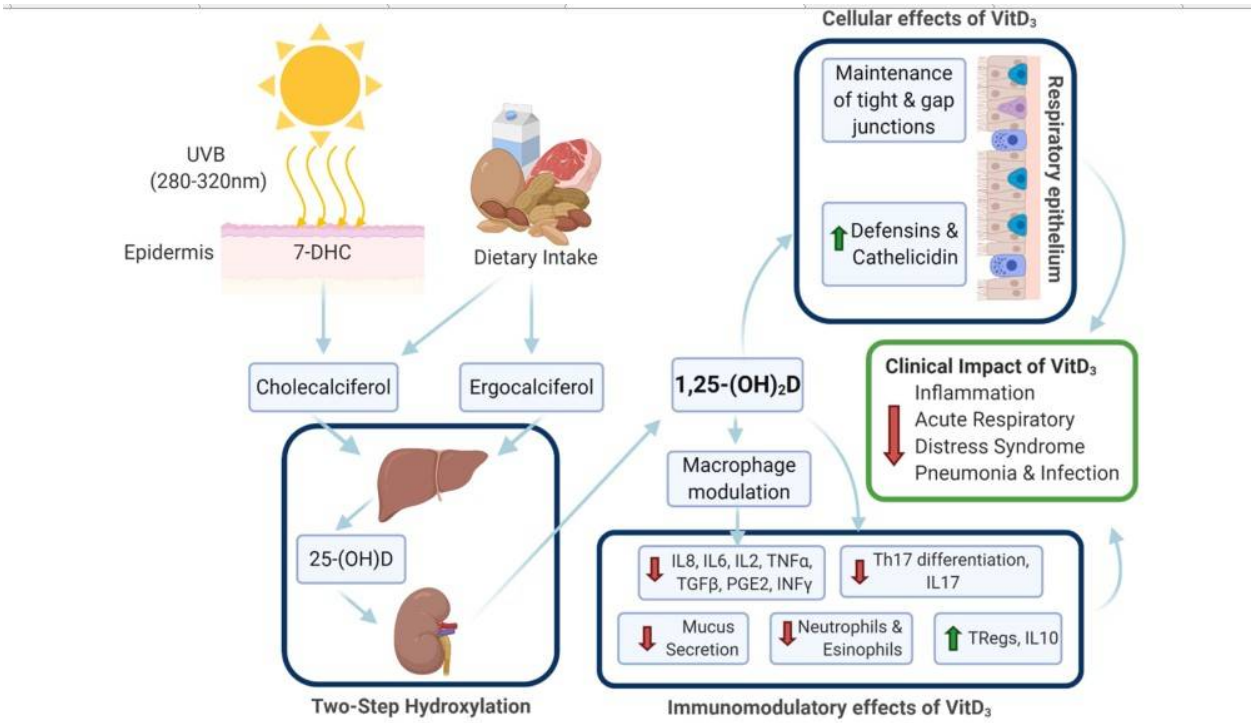

Fig. 2. Immunomodulatory actions of vitamin D.IL: interleukin; TNF: Tumor necrosis factor; IFN: Interferon; Th: T-Helper; 7-DHC: 7-Dehydrocholesterol; PGE2: Prostaglandin E2.

(Source: Shakoor et al., 2021, p. 4)

Grant et al.'s first publication focuses exclusively on applying Vitamin D supplements and reducing COVID-19 infections and deaths. Grant et al. (2020a) demonstrate that beginning with 10,000 IU of Vitamin D_3, followed by 5,000 IU per day over several weeks, reduces the risk of infection spread and avoids patient death. Epidemiological findings point to improved COVID-19 management when Vitamin D_3 supplements are introduced. However, results propose different Vitamin D_3 concentrations for unique viral infections. The study recommends the application of Vitamin D_3 in COVID-19 management to reduce conditions and their severity. However, the study integrates a table to summarize Vitamin D_3 dosage in various countries, demonstrating high dosage applied over time, improving patient outcomes. This research proves validity because the authors are affiliated with health research centers and rely on 157 peer-reviewed works. Thus, the study confirms that Vitamin D3 improves COVID-19 management.
Iddir et al.'s work focus on a dietary approach to COVID-19 management. Iddir et al. (2020) acknowledge that Vitamin D is instrumental in immune response because it interacts with cell entry receptors, such as the angiotensin-converting enzyme 2 (ACE2). The challenge is that this study focuses on all nutrients needed in the body instead of concentrating on Vitamin D and COVID-19. Nonetheless, the study demonstrates that the activated Vitamin D3 version readily interacts with specific nuclear receptors and regulates phosphorus and calcium chemicals in the body. However, the study only highlights a small portion of the information demonstrating a solid link in COVID-19 management. Moreover, only 14 of the 366 references used were associated with Vitamin D. (Iddir et al., 2020). Nevertheless, the evidence presented did confirm that dietary Vitamin D is vital in improving the body's immune system, albeit low relationship with COVID-19 management.
Radujkovic et al.'s work is a primary cohort study exploring a link between Vitamin D and COVID-19 management. Results indicate that patients with less than 12 ng/ml of Vitamin D in their system had a higher incidence of death compared with those with over 12 ng/ml (Radujkovic et al., 2020). The author relies on peer-reviewed articles to formulate the hypothesis and compare results with past studies. All authors are associates of the Department of Internal Medicine at the University of Heidelberg in Germany, giving the survey scholarly credibility. Furthermore, the study accommodates patients undergoing Vitamin D treatment, including those who died in the investigation process, eliminating bias in the results. Thus, the article illustrates a strong link between Vitamin D levels in the blood and COVID-19 severity among patients in Germany.
Mercola et al.'s work investigate Vitamin D, risk of contracting COVID-19, and disease severity. Different countries demonstrate that patients with less than ten ng/ml had a higher mortality rate or experienced severe COVID-19 symptoms.

Older adults were found to have a higher susceptibility because they had lower Vitamin D levels in the blood. The studies introduce proposed Vitamin D3 dosage for patients in different 25(OH)D levels, with those having 5-10 ng/ml requiring 300,000 IU compared with the ones with 16-30 ng/ml needing 100,000 IU as the initial dosage (Mercola et al., 2020). The study explains the source of variations in COVID-19 infection among African Americans, Hispanics, and white Americans. The partnership between individuals in the health sector and overreliance on 151 peer-reviewed works gives the work credibility. Therefore, the study illustrates that Vitamin D concentration in the body influences the severity of infection in the population.

Grant et al.'s second work explores the effect of Vitamin D supplements usage among athletes and reducing COVID-19 risk. The authors come from health and research institutions and rely on peer-reviewed work to support their assumptions and conclusion. The study indicates that dietary Vitamin D might be inadequate in meeting the daily requirements among athletes, thus the need for supplements. Statistical results confirm that supplements increase the body's 25(OH)D concentration and improve resilience against COVID-19. However, the study identified the prevalence of other risk factors, such as cardiovascular ailment, diabetes, pulmonary disease, and hypertension, for the reported higher mortality rates among Hispanic and African Americans. High 25(OH)D concentration improved recovery by 70% (Grant et al., 2020b). Thus, the article confirms that Vitamin D concentration affects recovery and disease severity.

Mohan et al.'s article also investigated the effect of Vitamin D deficiency on COVID-19 severity. The authors use diagrams in Figure 3 (A) to illustrate the virus' pathophysiology. Figure 3 (B) indicates the regular Vitamin D dual-action activates the innate and acquired immune responses. The two defense systems suppress lethal functions and supplement those that support the better defense. The article states that over 70% of the Indian population are Vitamin D deficient with less than 20 ng/ml concentration. Specifically, the phytate and phosphates in their diet are to blame for low dietary nutritional intake. The outcome is higher mortality and severe cases of COVID infection. The authors come from research institutions in New Delhi, India, and utilize peer-reviewed works to support their argument, giving credit to their work. Thus, this scholarly work confirms that Vitamin D deficiency is to blame for increased infection rates, severity, and the reported mortalities in the country.

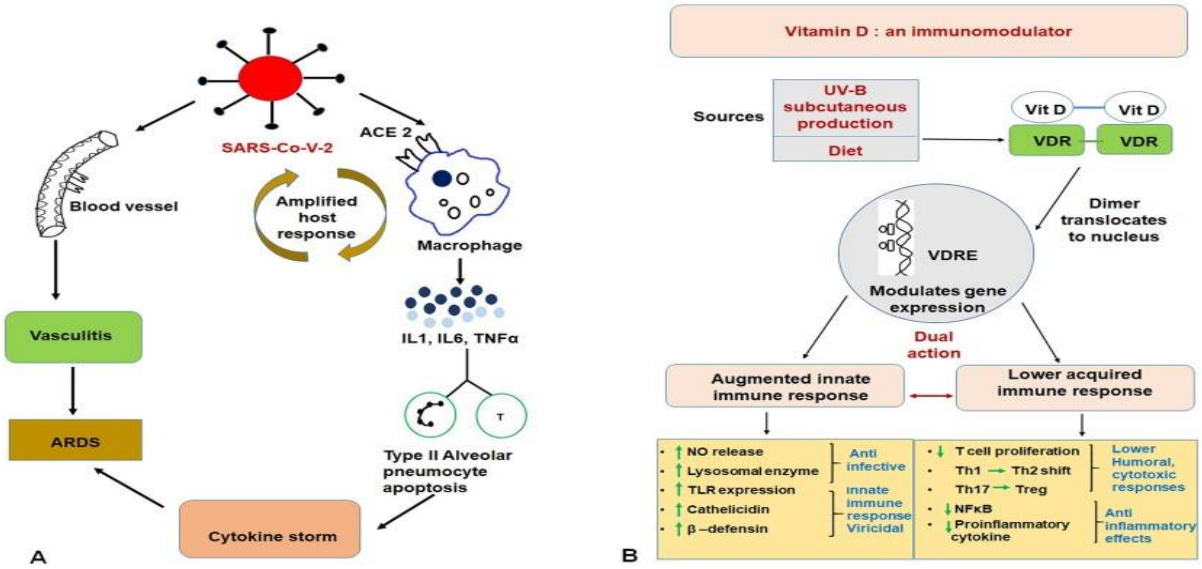

Fig. 3 – (A) COVID-19 Pathophysiology (B) Vitamin D's Dual Action on Immune Response
(**Source:** Mohan et al., 2020, p. 2)

VI. CONCLUSION

Vitamin D deficiency is strongly associated with severe COVID-19 symptoms and deaths, with supplements offering reprieve against the virus. This meta-analysis establishes reasonable grounds linking COVID-19 severity and mortality rate to Vitamin D concentration in the body. Mainly, the virus activates systems that damage organs and suppress the body's defense mechanism. For instance, ACE2 has a destructive presence in the body. In contrast, Vitamin D is shown to improve the body's immune response by supplementing innate and acquired immunity.

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AUTHOR CONTRIBUTIONS

Andrew J. Gonedes (Agonedes@Auburn.vcom.edu) and Dr. Gary Mount (gmount@Auburn.vcom.edu) analyzed the data, authored and reviewed drafts of the paper, approved the final draft.

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Additional Information and Declarations
The authors declare there are no competing interests.
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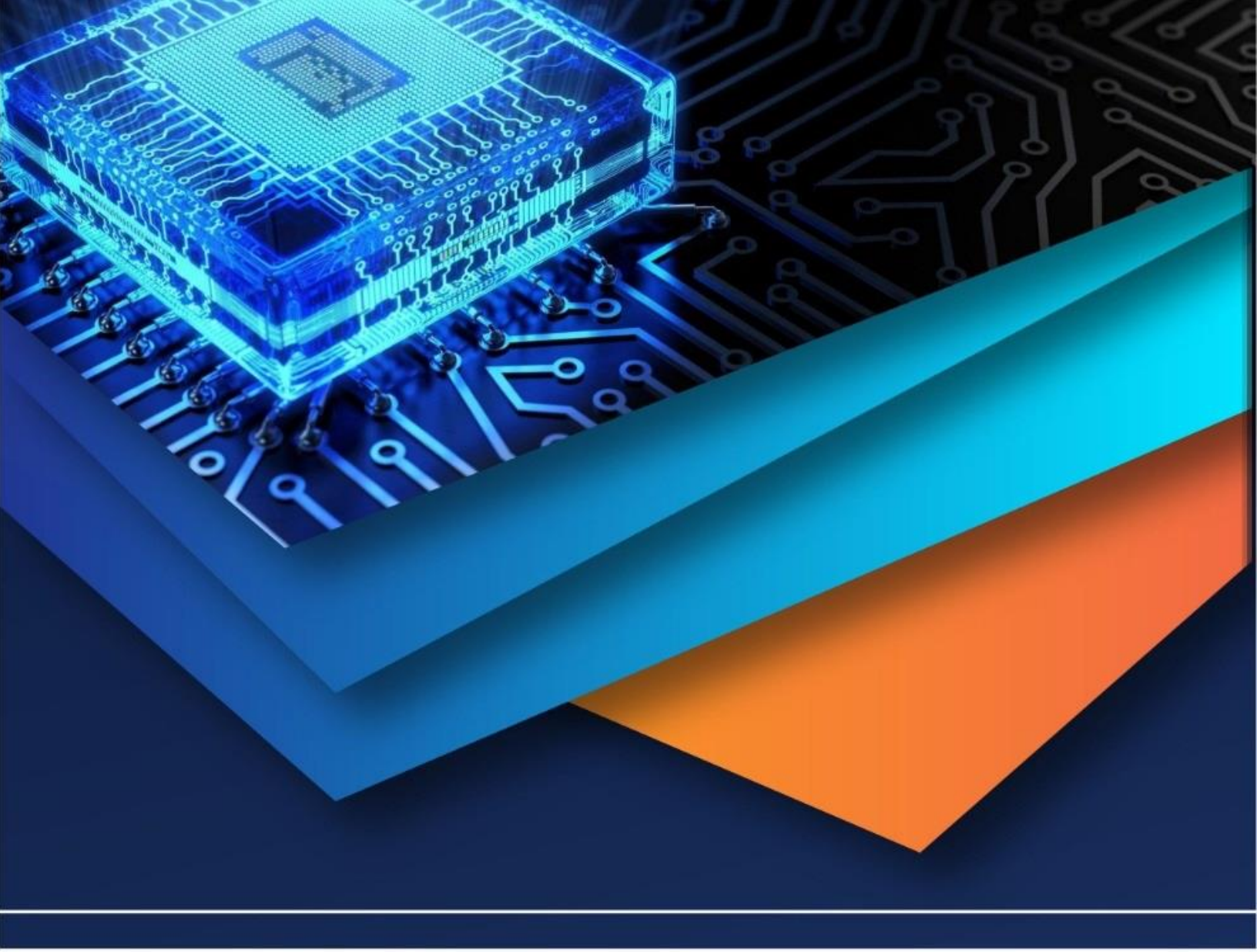

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