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REVIEW ARTICLE

Advances in Basic Medical Sciences

Vitamin D3, A Magical Solution in the Prevention of COVID-19

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ABSTRACT

OBJECTIVE: COVID-19 pandemic has grasped the whole world in a tight fix. For good public health, strict measurements should be adopted that can help minimize the infection and death risk during the pandemic. Threfore, present review discusses the postulated mechanism of protective role of vitamin D3 in decreasing the probability of having COVID-19 infections.

METHODOLOGY: The review data was gathered from july 2022 to july 2024 by sourcing relevant scientific literature from various databases using specific keyword combinations related to Vitamin D3 and COVID-19. A total of 515 research papers were reviewed; however, only 42 original articles from 2020 to 2024 specifically examined the relationship between Vitamin D and COVID-19.

RESULTS: The observational studies indicated a significant correlation between vitamin D levels and COVID-19. Conversely, randomized controlled trials suggested that high doses of Vitamin D3 could reduce mortality in COVID-19 patients.Vitamin D3 induces antimicrobial peptides for example cathelicidins (specifically LL-37) and defensins which may have antiviral activity and can reducing the concentration of pro-inflammatory cytokines while increasing the concentration of anti-inflammatory cytokines. Vitamin D3 boosts innate and adaptive immunity and suppresses renin-angiotensin pathway and stimulates ACE2 expressions.

CONCLUSION: On the basis of scientific literature, we can say that vitamin D3 is beneficial and required to augment the immune-modulatory effects on infected COVID-19 patients. Population-based studies debated between vitamin D3 levels and COVID-19 cases. But still, clinical trials and large epidemiologic and observational studies should be needed to assess these acclamations.

KEY WORDS: Vitamin D3; COVID-19; Magical solution; ACE2 receptors; AMPs

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INTRODUCTION

The coronavirus disease (COVID 19) responsible for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proclaimed the status of a worldwide pandemic from the World Health Organization (WHO) in March 2020. Yet, potential protective factors for this disease are still uncertain. Angiotensin converting Enzyme 2 (ACE2) is a close identical to ACE and negatively regulate the Renin-Angiotensin-Aldosterone System (RAAS). ACE removes two amino acids from the Carboxy terminus of decapeptide Angiotensin-I (ANGI) and generates an octapeptide Angiotensin-II (ANGII) whereas ACE2 splits ANG I into angiotensin-(1–9) and ANGII into angiotensin-(1-7). In this way, ACE2 counterpoises the functions of ACE. ACE2 is highly expressed in the healthy and diseased lungs. A study has revealed that ACE2 protects lungs from a severe acute injury and recently its role in COVID-19 pathology is well described.[1]

Vitamin D3 exerts noticeable effects on ACE2/Ang(1–7)/MasR axis with enriched ACE2 expression. The association between vitamin D levels and the severity/fatality caused by the COVID-19 was tested among various population and reported variable outcomes (Table 1). A study among European population identified that vitamin D deficiency among elderly who were considered as the most exposed group of the population for risk of COVID-19.[2] Another study among Chinese population revealed that vitamin D deficiency were more common among COVID-19 infected and severely ill patients.[3] Studies on Pakistani population exhibited a significant correlation

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between severe vitamin-D insufficiency and COVID-19 infection.[4,7] Interventional trials on large scale would be helpful in clarifying the role of vitamin D in COVID-19 infection and disease severity.

The data for this review was collected during July 2022 to July 2024 and was organized by gathering the pertinent scientific information from PubMed, Google Scholar, researchgate, Web of Science using the key words with all possible combinations "Vitamin D and CoVID-19", "Vitamin D and SARS-CoV-2", " Vitamin D and ARDS", "Role of Vitamin D and CoVID-19", and "Molecular mechanism of Vitamin D and CoVID-19". We have surveyed a total of 515 published research papers. Out of this, only 42 original articles published during 2020 to 2024 the association or effect of vitamin D on COVID-19. Research evidences regarding influence of vitamin D in other diseases, and other viral manifestations were excluded.

The Pathogenic Mechanism Of Sars-cov-2

SARS-CoV-2 share 79% structural homology to the SARS-CoV uses ACE2 as a receptor like SARS-CoV, because the receptor binding domain (RBD) of SARS-CoV-2 of spike protein (S-Protein) is similar to the SARS-CoV. A structure model analysis has shown that SARS-CoV-2 has the 10 folds higher binding affinity with ACE2 as compare to the SARS-CoV.[35] The S-protein consists of two components: the S1 subunit which is responsible for interacting with the host entry receptor ACE2, and the S2 subunit which facilitates the membrane fusion.[36] The two subunits are demarcated by the S1–S2 site, having a furin cleavage motif that undergoes the cleavage within virus producing cells. Subsequent to the attachment to ACE2 on the target cells such as multiciliated cells found in the nasopharynx or trachea, as well as sustentacular cells located in the nasal olfactory mucosa,[37]the S-protein is cleaved by the transmembrane serine protease TMPRSS2 at the S2′ site.[38] Upon cleavage, the S2 subunit trimers are stimulated to facilitate the fusion of viral and host lipid bilayers, leading to the discharge of the viral ribonucleoprotein complex within the host cell would infect humans and develop COVID-19. Therefore, how robust the communication is for risk of human transmission and what is the pathological mechanism which causes organ damage are still unclear.

In brief, SARS-COV-2 has higher affinity to binds with the ACE2 than SARS-CoV. RBD in S-protein of SARS-COV-2 binds with ACE2 receptor in respiratory epithelium would infect human leads to the development of COVID-19.

Roles of Vitamin D3 in COVID-19

Vitamin D3 [1,25-(OH)2D3] acts locally in immune cells (such as T cells (CD4+ and CD8+), B cells, monocytes, neutrophils, macrophages, and dendritic cells)[39] where it arrives inside the nucleus and sticks to nuclear vitamin D receptor (VDR) that initiates the regulatory sequence adjacent to the target genes. An eminent role of Vitamin D3 is the calcium homeostasis along with other important body functions.[40] Vitamin D3 has been confirmed to decrease the risk of getting a common cold. It also improves cellular immunity, adaptive immunity, and antioxidation-related genes' expression. Individuals with a deficiency in vitamin D demonstrated increased expression of IL-6, while TNF-α was observed to stimulate monocyte phenotypes.[41]Host reactions may sometimes be modified due to excessive exposure to inflammatory agents, leading to a significant manifestation known as the "cytokine storm" which results in severe complications in patients infected with SARS-CoV-2. [42] Immune responses can be improved by vitamin D3 supplements which maintain equilibriums between inflammatory versus anti-inflammatory processes. Vitamin D deficiency persist worldwide affecting more than 1 billion individuals of the globe.43This persistent vitamin D deficiency leads to different pathological states including various systemic infections along with several other disorders.[44,45] The deficit Vitamin D modifies the immunity of body due to its crucial role in the regulation of body's immune response by affecting the antiviral proteins secretions therefore enhances the innate immunity, which preserve the mucosal integrity and defense mechanisms.[46, 47] Henceforth, researchers proposed the therapeutic role of Vitamin D3 against COVID-19 (Table 2). However, to date, limited studies have conducted to describe the beneficial effect of Vitamin D3 with the clinical consequences caused by COVID-19. Further investigations regarding Vitamin D supplementation and its beneficial effects in boosting the immune system and mitigating the transmission of SARS-CoV-2 are needed. Thus, it is hypothesized that vitamin D3 may be able to fight with the novel coronavirus COVID-19. A single dose of vitamin D3 (300,000 IU) was suggested by a recent study for the better prevention and cure of CO0VID-19.[48]

In brief, vitamin D boosts the immune system which may become a significant factor for the prevention of infection. However, fewer published data is available relating to the successful prevention of infection by vitamin D.

Vitamin D3 has strong antiviral activity and the precise role of vitamin D3 against viral infection is given in following manners which could be same in the prevention against COVID-19.

Vitamin D3 as a modulator of innate and adaptive immunity in COVID-19 patients

Vitamin D and its intracellular receptor VDR forming the complex with the retinoid X receptors (RXR) activation, resulting in the binding of whole complex within the VDR response element (VDRE) on the promoter region of genes and control the activity of several genes, such as β-defensins and

S.No	Study	Place	Data collection Period	Study design	Cases	Controls	Outcomes
1	Abdollahi et al. 2020 [8]	Tehran, Iran	February – April 2020	Case Control study	201	201	Significant correlation was observed between low vitamin D status and COVID-19 susceptibility.
2	Anjum et al., 2020 [4]	Rahim Yar Khan. Pakistan	March - June 2020	Prospective/ Observational	140	-	A significant correlation existed between severe vitamin-D insufficiency and the mortality among patients suffering from covid-19 infection.
3	Ansari et al., 2020 [5]	Larkana and Gambat	March 2020 - August 2020	Cross-sectional/ Observational	125	-	Strong relationship was found in between severe vitamin-D deficiency and mortality among covid-19 disease
4	D'Avolio et al., 2020 [9]	Switzerland	-	Cohort	187	-	Lower vitamin D was found among COVID 19 as compared to controls
5	Hastie et al., 2020 [10]	England, Scotland and Wales	2006-2010	Not defined	348,598	-	No association was found between Vitamin D and contracting CoVID 19
6	Mendy et al., 2020 [11]	USA	March - May 2020	Cross Sectional	689	-	Vitamin D Deficeincy was linked with the prolong hospital stay and disease severity
7	Merzon et al., 2020 [12]	Israel	Febuarary - April 2020	Cohort	7,807	-	Low plasma vitamin D was present in patients as compare to controls
8	Radujkovic et al., 2020 [13]	Heidelberg	March - June 2020	Not defined	93	-	A correlation between Vitamin D insufficiency and the severity/fatality of COVID-19
9	Raharusun et al. 2020 [14]	Indonesia	March - April 2020	Retrospective Cohort	780	-	COVID related mortality was 10.12 times higher among vitamin D deficient patient as compare to normal vitamin D status
10	Ye et al., 2020 [15]	China	February – March 2020	Case-Control Study	62	80	Vitamin D deficiency emerged as a significant risk factor in the context of severe and critical COVID-19 cases
11	Asghar et al., 2021 [6]	Karachi, Pakistan	May - November 2020	A retrospective study	91	-	Adequate 25(OH)D levels exhibited a reduced occurrence of invasive procedures, complications, and mortality
12	Butler-Laporte et al., 2021 [16]	11 countries of Europe	July - December 2020	A Mendelian randomization study	14134	1,284,876	No conclusive findings were noted to correlate the vitamin D with COVID-19 susceptibility.
13	Campi et al., 2021 [17]	Milan, Italy	March - April 2020	Not defined	103	206	Vitamin D levels were inversely correlated with IL-6 levels and were independent predictors of COVID-19 severity and mortality.
14	Demir et al., 2021 [18]	Tokat, Turkey	November 2019 – November 2020	Retrospective cohort study	27	260	High vitamin D levels was shortened the hospitalization and alleviate the intensity of COVID-19

15	Fatemi et al., 2021 [19]	Tehran, Iran	October 2020 - May 2021	a prospective observational study	248		A probable correlation existed in between insufficient vitamin D levels and elevated mortality rates among COVID-19 patients.
16	luo et al., 2021 [20]	Wuhan, China	February - March 2020	Cross-sectional study	335	-	Vitamin D deficiency influences hospitalization and COVID-19 severity
17	Katz et al., 2021 [21]	Florida, US	October 2015- June 2020	Not defined	887	-	Significant association was found between vitamin D deficiency and COVID-19 risk.
18	Samimagham et al., 2021 [22]	Iran	-	Cross-sectional study	48		A significant correlation present in between insufficient vitamin D levels and the severity of illness and mortality rate among COVID-19 patients
19	Kalichuran et al., 2022 [23]	Johannesburg, South Africa.	September 2020 - February 2021	Prospective, cross-sectional descriptive study	100	-	A considerable vitamin D inadequacy and insufficiency heightened the susceptibility of COVID 19
20	Nielsen et al., 2022 [24]	Denmark	May-20	Observational study	447	-	Decreased vitamin D were linked to an elevated likelihood of experiencing severe manifestations of the COVID-19 disease.
21	Seal et al., 2022 [25]	San Francisco, California	Nov - Dec 2020	Retrospective cohort study.	4,599	-	Vitamin D have an independent correlation with hospitalization and mortality related to COVID-19
22	Subramanian et al., 2022 [26]	Liverpool, UK	March - November 2020	Observational study	472	-	No significant relationship was found between 25(OH)D deficiency (<50 nmol/L) and mortality from COVID-19
23	Ahmad et al., 2023 [27]	19 European countries	March 2020 - June 2023	Observational study	-	-	A statistically significant negative correlation between 25(OH) vitamin D average levels and COVID-19 mortality.
24	Basińska-Lewandowska et al., 2023 [28]	Lodz, Poland	March – April 2020	Not defined		134	An elevated likelihood of COVID-19 was solely noted among those exhibiting a profound deficiency of 25OHD (<12 ng/mL).
25	Filippo et al., 2023 [29]	Milan, Italy.	August - November 2020	Observational cross-sectional retrospective	50	50	The efficacy of vitamin D supplementation in preventing COVID-19 complications warrants investigation through randomized controlled trials.
26	Jalalzadeh et al., 2023 [30]	USA	March 2020 - December 2021	Retrospective study	452	-	no significant differences was noted in between COVID 19 and Vitamin D status of the participants.

27	Konikowska et al., 2023 [31]	Wroclaw, Poland	February 2020 - June 2021	Not defined	474	-	A correlation was found between the 25(OH)D levels and COVID-19 and their subsequent hospitalization trajectory as well as mortality risk.
28	Mahmood et al., 2023 [7]	Karachi, Pakistan	Not defined	Cross-sectional study	80	-	Insufficient 25-hydroxyvitamin D levels exhibited lower results and prolonged stay in hospital.
29	Zeidan et al., 2023 [32]	Cairo, Egypt	October 2020 - March 2021	Prospective multicenter study	180	200	Vitamin D insufficiency could potentially serve as autonomous risk elements for the predisposition to COVID-19
30	Afshar et al., 2024 [33]	Shiraz, Iran	January - March 2022	A case-control study	46	52	No signficant association was present between Vitamn D and COVID-19 severity
31	Noraldinvand et al., 2024 [34]	Tehran, Iran	Jan - March 2021	Case Control study	50	50	Vitamin D serves as a viable protective element in combating COVID-19 transmission

Table 1: Association between Vitamin D3 and CoVID-19

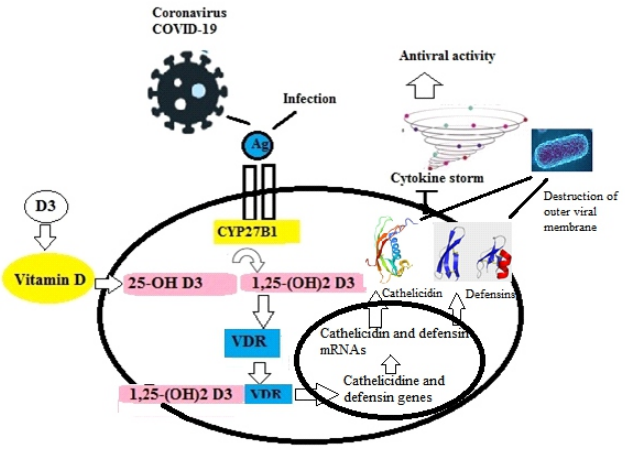

Figure 1. Mechanism of action of vitamin D3 and cathelicidin (ll-37) in the prevention of viral infection such as COVID-19.

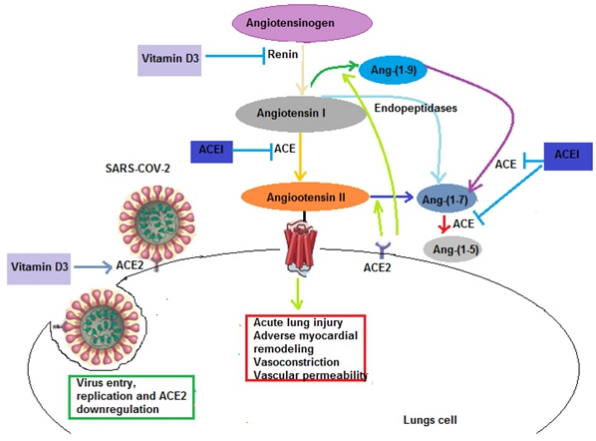

FIGURE 2. INTERACTION BETWEEN VITAMIN D3, SARS-COV-2 AND THE RAAS PATHWAY.

cathelicidin.[59] Vitamin D augments the innate immunity by upregulating the two main categories of amphipathic AMPs detected at the mucosal lining of the human respiratory system include cathelicidins and both type of defensins.[60] Cathelicidins are the distinct group of AMPs and LL-37 is one of the major representatives of Cathelicidin present in the mucosal lining of human airways and has an antiviral activities. Cathelicidin triggers the inflammatory pathway and stimulating the chemotaxis of leukocytes which helps to engulf the pathogens from the airways by the apoptosis and autophagy in exposed respiratory epithelium to the virus.[46,61] Vitamin D also involves in the regulation of Alpha and Beta defensins, which directly abolish the viral membrane;

The previous report suggests that respiratory viruses increase VDR expression in human airways epithelial cells which kickbacks the antiviral feedback[62] such as COVID-19 to exogenous vitamin D3 (Figure 1).

Binding antigens to the toll-like receptors (TLRs) excite CYP27B1 and activated vitamin D3 which in turn binds to its receptor VDR and form D3-VDR complex which triggers the transcription of cathelicidin (LL-37) and alpha and beta Defensins and promote antiviral activity.

Similarly, Vitamin D3 also boosts cellular immunity influenced

S.No	Study	Place	Data collection Period	Study design	Cases	Controls	Outcomes
1	Meltzer et al., 2020 [49]	Chicago	March - April 2020	Retrospective cohort study	489	-	A potential influence of vitamin D3 with COVID-19 susceptibility.
2	Rastogi et al., 2020 [50]	North India	Not Described	Randomised, placebo-controlled study (SHADE Study)	16	24	High doses of Vitamin D3 prevents SARS-Cov-2 along with the notable reduction in fibrinogen levels.
3	Annweiler et al., 2022 [51]	Angers, France	Not Described	A multicenter, open-label, randomized controlled trials	254	-	High-dose vitamin D3 could improve overall mortality among COVID 19 patients
4	Cervero et al., 2022 [52]	Madrid, Spain	Not Described	Multicenter, single-blinded, prospective randomized pilot clinical trial (RCT)	87	-	High dose of Vitamin D3 could potentially improve oxygen consumption needs among COVID-19 patients
5	Hafezi et al., 2022 [53]	Dubai	September 2020 - January 2021	In vitro and investigation study	80	-	Vitamin D3 augments the interferon (IFN α/β) signaling pathway and may possibly alleviate the COVID-19 severity by enhancing the innate immunity
6	Oristrell et al.,2022 [54]	Barcelona-Central Catalonia	April 2019 - February 2020	A population-based, cohort study	4643139	-	Serum vitamin D3 levels of at least 30 ng/ml exhibited a correlation with improved outcomes of COVID-19.
7	Sarhan et al., 2022 [55]	Cairo, Egypt	December 2020 - June 2021	A Randomized Clinical Trial	116	-	High-dose vitamin D3 treatment alleviates the cytokine storms and demonstrated reduced incidence of adverse consequences Covid 19 .
9	Kirby et al., 2023 [56]	Arizona, USA	Not Described	Pilot study	40	-	Decrease Vitamin D3 have been linked with a prolong duration and increased Covid-19 Severity.
10	Dilokpattanamongkol et al., 2024 [57]	Thailand	July 2020 - March 2022	A single-center randomized controlled trial	294	-	Vitamin D3 supplementation along with the conventional therapy could potentially confer benefits upon individuals suffering from COVID-19 pneumonia.
11	Singh et al., 2024 [58]	North India	Not Described	Randomized, double-blind, placebo-controlled study (SHADE-S)	90	-	Administration large doses of Vitamin D3 may lead to a decrease in mortality among COVID-19 ptients

Table 2: Therapeutic role of Vitamin D3 against CoVID-19 Pneumonia

by innate immunity which produces pro and anti-inflammatory cytokines against infections caused by viruses and bacteria, as observed in COVID-19 cases.[63] Vitamin D3 can help in reducing the production of pro-inflammatory T helper cell type 1 (Th1) cytokines, such as tumour necrosis factor (TNF) and interferon (INF). Vitamin D3 also suppresses responses mediated by the Th1 cell initially by limiting the inflammatory cytokines IL-2 and INF-γ production. Moreover, D3 stimulates cytokine production by Th2 cells which supports Th1 cells overpowering indirectly with actions arbitrated by a crowd of cell types. Likewise, D3 promotes anti-inflammatory T regulatory cells induction, thus impeding inflammatory processes reported having main functions in the ALI treatment.[64] Additionally, VDR mediates the activities of vitamin D3 which inhibits angiopoietin-2-TEK receptor tyrosine kinase-myosin light-chain kinase pathway and be a safeguard against sepsis-induced lung injury. All of these indicated a potentially useful effect of vitamin D3 on lung injury may be caused by the bacterial, microbial and viral infection such as COVID-19.

In brief, Vitamin D/VDR/RXR complex regulates β-defensins

and cathelicidin genes in human airways and enhancing innate immunity. Vitamin D up regulates the cathelicidin which triggers the inflammatory processes and engulf pathogens. Vitamin D also mediates defensins to combat viral membranes. . Respiratory viruses upsurge VDR expression in airway epithelium, eliciting antiviral reaction like in COVID-19 patients. Vitamin D3 improves cellular immunity against infections, reducing pro-inflammatory and stimulating anti-inflammatory cytokines. Vitamin D/VDR complex inhibits pathways that cause sepsis induced lung injury. In short, Vitamin D3 displays potential benefits in treating lung injuries caused by infections.

Vitamin D3 as a modulator of RAAS pathway among COVID-19 patients Vitamin D3 is a negative endocrine proprietor of RAAS. Normal vitamin D3 levels can lower RAAS activity via suppression of renin expression. RAAS activity is intrinsically higher in lungs, where the ACE2 expression is high as well, responsible to stabilize the production of ACE along with A-II which means that the risks are higher here in the lung. This can also be the mechanism when SARS-CoV-2 causes down regulation of ACE2. However, failure of ACE2 function can be a critical event which leads to increased neutrophil infiltration in the lung resulting in the exaggerated inflammation and injury. Once the ongoing lung infection results in hypoxia, the risks are further higher by the generation of renin that can lead to a vicious circle. Vitamin D3 inhibits the renin activity[65] and stimulates the ACE2 expression [66] by which it can prevent the COVID-19 (Figure 2). However, whether vitamin D3 may affect COVID-19 by regulating RAAS remains to be investigated.

In brief, Vitamin D3 lowers RAAS by reducing renin expression, which is higher in the lungs. This can lead to increased inflammation and injury with in the lung. Vitamin D3 inhibits renin activity and stimulates ACE2 expression, potentially preventing COVID-19. However, the impact of vitamin D3 on COVID-19 by regulating RAAS remains to be investigated.

RECOMMENDATIONS

Vitamin D3 supplements should be administered, which may be a cheap and easy step towards prevention of COVID-19 infection and its spread. Previous reports suggested different doses of vitamin D3 among different ethnic populations.67,68 Vitamin D therapy is necessary when hospitalized patients with SARS-CoV-2 infection have baseline plasma concentrations lower than 30ng/mL (ideal 40–60ng/mL), particularly if the baseline level is 10ng/mL Although it is impossible to verify the baseline 25(OH)D concentrations among infected patients, it is advised to take 2000–3000 oral IU daily.

CONCLUSION

Vitamin D3 deficiency may increase susceptibility to COVID-19 infection by impairing immune function. This is especially troublesome for many old age citizens, who are vitamin D3 deficient, are the greatest risk of developing more serious COVID-19-related Complications. Exogenous Vitamin D3 supplementations are an affordable and safe strategy which may lessen the disease progression and its complications via AMP promotions, immune system modulation and RAAS modulation could be added to the existing standard treatment. Further investigations are needed to conduct a randomized controlled trial and population-specific studies to confirm the correlation between D3 supplementation and COVID-19 infection prevention.

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CONFLICT OF INTEREST

Author declared no conflict of interest

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AUTHORS CONTRIBUTIONS

MI: Conception, Design of the work, Data collection, and Drafting, Reviewed, Final approval, Agreement to be accountable.

AA: Conception, Design of the work, Acquistion, Data Analysis, and Drafting, Reviewed, Final approval, Agreement to be accountable.

SSF: Conception, Design of the work, Interpretation of data for the work, and Drafting, Reviewed, Final approval, Agreement to be accountable.

TAK: Conception, Design of the work, Data collection, and Drafting, Reviewed, Final approval, Agreement to be accountable .

DATA SHARING POLICY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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