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Vitamin 25 OH- D Status in Moderate and Severe COVID-19 Patients: A meta-analysis Study

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ABSTRACT

Background: In 2019, WHO declared that covid-19 was caused by the SARS- Co-V-2 virus. In many articles from the various journals, it is observed and concluded that, there is an inverse association between the serum calcitriol levels in moderate and severe covid-19 patients. So little know about the association, a systematic review and meta-analysis of seventeen studies were taken in to consideration. The aim of the article is to study the correlation between serum calcitriol level and COVID-19 infections in moderate and severe covid conditions.

Method: The Meta-analysis, a systematic review is to determine sr. vitamin-D in moderate and severe covid-19patients. The study was conducted under PRISMA guide lines without language restrictions. The articles were identified through Pub Med (U.S. National Library of Medicine,USA.), Bio-Med, Med line, PLoS ONE, Web of Science, LILACS (Latin American and Caribbean Health Sciences Literature), Web of Science, Europe PMC, Bio-sis Previews, Chemical abstract services-(CAS), Elsevier Properties USA. The studies have been considered which were published before 25th Dec. 2022. MAIN OUTCOME MEASURES: Association between the serum calcitriol levels in moderate and severes covid-19 patients.

SAMPLE SIZE: (Total 2673) moderately affected1316 and severely affected 1297 patients from 17 articles.

Results: Screened out and selected 17 studies from 954 articles. Among 17 articles, thirteen articles were showing highly significant variations, and only 4 articles were statistically not

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significant, and the combined estimation of this Meta-analysis study showed highly significant, since *P< .0000.*

Conclusion: The study concluded that, there is a negative association between serum vitamin 25OH-D levels in moderate and severe covid-19 patients.

Keywords: Meta-analysis, Vitamin 25OH-D, Moderate-Severe, Covid-19 Disease.

INTRODUCTION

Corona virus infection causes to a healthy individuals called as COVID-19 disease. It is a major pandemic spreading rapidly and now a leading cause of death worldwide. Currently, there was no drugs or vaccines available to treat the infected patients of this disease. So, there was the only prevention and social distancing are the ways to prevent this disease from community transmission. [1]

Vitamin 25OH-D is an important micro-nutrient that has been reported to improve immunity and protect against respiratory diseases. This review of serum calcitriol highlights the important scientific coordination between vitamin D levels and susceptibility to COVID-19 patients. So serum vitamin 25 OH-D will varies in moderate and severe COVID-19 patients.[1]

Scientist Mitchell F. et al and health authorities had been discussed about the possibility that vitamin D levels might represent an important and useful intervention to strengthen the immune system and will help in the fight against COVID-19. [2]

Some observational studies reported the independent associations between low concentration of 25-hydroxy vitamin D and susceptibility to acute respiratory tract infections [3].

The scientist Sun et al. (2020) were found that 74% of patients admitted for severe COVID-19 had decreased levels of serum Ca^{++}, vitamin25 OH-D and hypoproteinemia, so for these reasons they could advice that hypocalcemia is a biomarker of clinical severity for the diagnosis and prognosis of covid-19 patients. [4]

Since vitamin 25-OH-D is associated with calcium deficiency and the immune chemical activities of innate and adaptive immune systems, as well as inflammation in covid-19 cases.

In some observational studies it was showed that, an inverse relationship has been found in between serum 25-hydroxy vitamin D concentrations and the risk or severity of covid-19 virus disease. There were several reactions have been stated for the importance of vitamin D in covid-19 patients, including modulation of immune and inflammatory responses and regulation of renin- angiotensin-aldosterone system. Decreased concentration of serum vitamin 25OH-D might be found in predisposed, severe and patients of covid-19 disease. [5]

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So, the meta-analytic study of serum vitamin 25OH-D variations in COVID-19 patients were taken in to consideration for this research article.

AIM AND OBJECTIVES: The aim and objective of the study is to perform the systematic review and meta-analytic study of Sr. vitamin 25OH-D in moderate and severely infected COVID-19 patients.

MATERIAL AND METHODS

Literature search and setting strategy:

Meta-analysis was done by searching of published studies which were reporting the "Serum vitamin 25 OH-D level status in moderate and severe COVID -19 patients " that was undertaken in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISM) statement for the systematic reviews of international studies were followed. [8] The three stages comprehensive search of the literature was conducted in the following data bases; (U.S. National Library of Medicine, USA), Web of Science, PLoS ONE.org, www. Blood Journal.org, Europe PMC, Chemical Abstract Services-(CAS), Bio sis Previews, Elsevier Properties S.A., USA. The studies published before 25th December 2022 was to be selected and considered for the Meta-analysis study.

The first stage of the study was included the necessary databases, which was searched out by using the different concerned search criteria. The Pub Med® database were searched by using the MesH® (Medical Subject Headings) term`` COVID-19 patients " and the key words ``Serum vitamin 25 OH- D level " The Web of Science® databases were searched by using the terms 'moderate and severe COVID -19 patients 'and 'vitamin 25OH- D level'. The PLoS ONE® database were searched by simply typing the title name on the Google internet. The blood journals were searched simply by typing the name of the journals, and then title name of the research topic on internet. In the above mentioned journals, published results were limited to covid-19 studies and information. The results obtained from books, editorials, commentaries and conference proceedings were excluded from the studies.

In second stage, the ideas obtained for reaching the databases using above research criteria was screened by reading the article 'TITLE' and 'ABSTRACTS'. Studies which were not related to topic or not satisfying the inclusion criteria that were excluded. Third stage is meant for the manuscript screening, and manually searching the data and references for addition. In this stage, articles not satisfying the inclusion criteria were excluded. We excluded literature reviews, cross-sectional studies, studies on animals, articles with missing data, and

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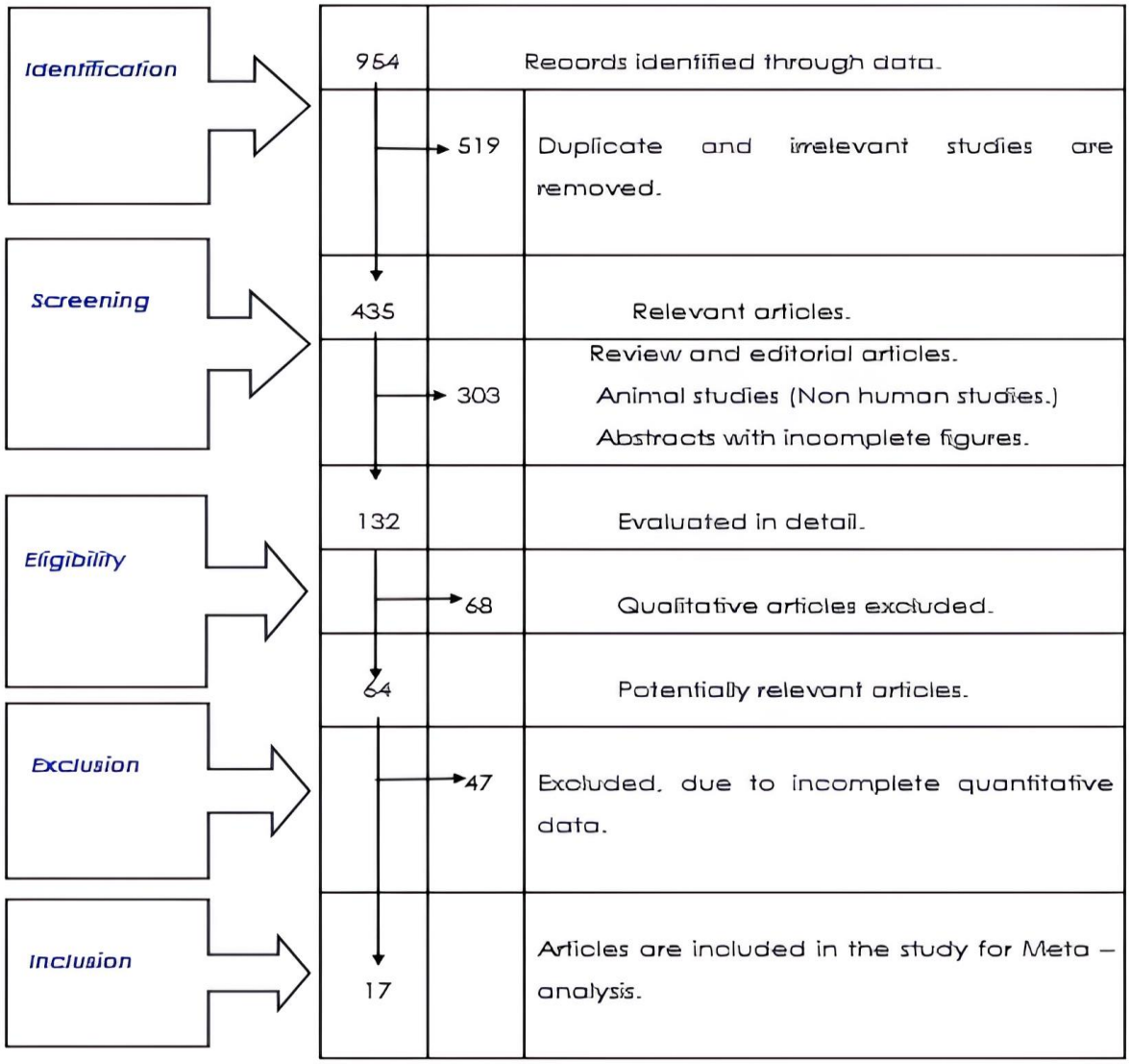
excluded the qualitative estimated values of serum vitamin 25 OH- D levels in moderate and severe covid-19 patients.

INCLUSION AND EXCLUSION CRITERIA: The inclusion and exclusion search procedures were conducted independently by the reviewer and the final appropriate group of articles were included in this meta-analysis study.

STUDY DESIGN:

Table: 1. Selection of studies for Meta- analysis of vitamin 25OH- D level in moderate and severe COVID -19 patients



The search was conducted by identifying the articles up to 25 th Dec. 2022.

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Data extraction and Analysis:

Data extraction:

Data extraction had been conducted independently by 2 authors, using a standardized data extraction form. To resolve the discrepancies, we have been consulted to the statistician and extracted the information of the vitamin 25OH- D level in moderate and severe COVID -19 patients, it was carried out on the basis of title, authors, publication year, and name of study.

Statistical analysis:

In this the meta-analysis study, seventeen studies was included by examining the different levels of serum vitamin 25 OH-D levels in COVID-19 patients in various but that should be related in moderate and severe COVID -19 diseases, statistical analysis had been carried out manually in case of processed variables and partly calculations was carried out by using the latest SPSS-24 software version and Microsoft excel.

For the study analysis purpose, we have been considered mean values, standard deviations, sample size, and number of cases and controls, and then the calculation of student‘t` test was applied. The statistical graphs had been represented by using the Microsoft excel software, and at the end of the calculation, the $P<.05$ was considered to be statistically significant.

MAIN OUTCOME MEASURES:

The study showed that, there is a negative association between the serum calcitriol levels in moderate and severes covid-19 patients.

RESULTS

About seventeen comparative studies were screened out from nine hundred fifty four (954) published articles from various research publications. The final screened data obtained from seventeen articles were considered for the present analysis.

The total number of SASR Covid-19 infected patients obtained from the above seventeen articles were two thousand six hundred seventy three (2673). From that, moderately affected patients were thirteen hundred sixteen (1316) and severely affected SASR Covid-19 patients were twelve hundred ninety seven (1297) in numbers.

In this meta-analysis statistical data, the sample size, mean and standard deviation were considered for the comparison in between the moderately affected and severely affected SASR Covid-19 patients. In this study, among these seventeen articles, research article number one, eleven, thirteen and article number seventeen were found non significant, and remaining

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thirteen articles were showed highly significant, that means the serum vitamin 25OH- D levels are found significantly decreased in severely affected SASR Covid-19 patients as compared to moderately affected Covid-19 patients.

Table: 2. Vitamin-D status in moderate and severe COVID-19 patients

Sr. No.	Authors	Number of Patients (N)	Vita 25OH- D in Moderate Covid-19 Cases (ng/L)	Vita 25OH- D in Sever Covid 19 Cases (ng/L)
			Mean ± SD	Mean± SD
1	Alex Pizzini et al (2020)	87(34+53)	125.7 (47.42)	124.8 (59.9)
2	Emilija Atanasovska et al (2021)	33 (15+18)	28.47 (3.05)	18.39 (2.29)
3	Emilija Atanasovska et al (2021)	33 (24+9)	39.46 (3.472)	18.05 (1.28)
4	Antonio D. Avolio et al. (2021)	73 (41+32)	25.9 (2.28)	17.2 (1.3)
5	Antonio D. Avolio et al. (2021)	74 (56 + 18)	22.0 (2.1)	11.1 (1.21)
6	Anshul Jain et al., (2020)	154 (91+63)	27.89 (6.21)	14.35 (5.79)
7	A. Catharine Ross et al.,(2021)	212 (100+112)	31.2 (3.24)	17.1 (2.32)
8	Mustafa Demir (2021)	176 (80 + 96)	13.51 (0.40)	6.52 (0.19)
9	Bagcilar Egitim ve Arastirma Hastanesi (2021)	137 (34+103)	26.3 (8.4)	10.1 (6.2)
10	Irene Campi et al., (2021)	155 (52+103)	30.3 (8.4)	18.2 (11.4)
11	Irene Campi et al., (2021)	155 (52+103)	18.8 (11.7)	18.7 (11.6)
12	Pizzini Aet al (2021)	109 (22+87)	18.45 (8.9)	14.42 (6.92)
13	Nirav Nimavat et al (2021)	36 (9+27)	20.3 (12.0)	19.0 (16.1)
14	Amiel A. et al (2022)	87 (74 +13)	26.65 (12.96)	6.33 (3.96)
15	Jain et al. (2020)	164 (69 + 95)	27.9 (6.2)	4.4 (5.8)
16	Yvette C. Cozier et al., (2021)	885(512+ 373)	24.5 (1.98)	18.0 (1.0)
17	Luigi Gennari et al., (2020)	103 (51+52)	22.4 (14.4)	19.3 (13.2)

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Table no:3. Showing SMD and 95% LCI-UCI in moderate and severe COVID -19 cases

Sr. No.	Authors and Year	SMD	95% CI = (LCI - UCI)
1	Alex Pizzini et. al. (2020)	0.9	CI = -13.7 - 15.5
2	Emilija Atanasovska et. al. (2021)	10.08	CI =8.73 - 11.43
3	Emilija Atanasovska et al. (2021)	21.41	CI = 20.13 - 22.69
4	Antonio D. Avolio et al. (2021)	8.7	CI = 8.09 -9.31
5	Antonio D. Avolio et al. (2021)	10.7	CI =10.35 - 11.45
6	Anshul Jain et al., (2020)	13.54	CI = 12.21 - 14.87
7	A. Catharine Ross et al.,(2021)	14.1	CI = 13.57 - 14.63
8	Mustafa Demir (2021)	6.99	CI = 6.89 - 7.09
9	Bagcilar Egitim ve Arastirma Hastanesi et al. (2021)	16.2	CI = 13.56 - 18.84
10	Irene Campi et al., (2021)	12.1	CI = -8.57 - 15.63
11	Irene Campi et al., (2021)	0.1	CI = - 3.78 - 3.98
12	Pizzini Aet al (2021)	4.03	CI = 0.56 - 7.5
13	Nirav Nimavat et al (2021)	1.3	CI = 3.59 - 6.19
14	Amiel A. et al (2022)	20.32	CI = 13.08 - 27.56
15	Jain et al. (2020)	23.5	CI = 21.64 - 25.36
16	Yvette C. Cozier et al., (2021)	6.5	CI = 6.28 - 6.72
17	Luigi Gennari et al., (2020)	3.1	CI = - 2.27 - 8.47
18	Combined estimation	10.91	CI = 10.1 - 11.81

The independent sample ‘t’ test and pooled standard deviation of moderate and severe covid-19 patients was carried out. The calculations were completed by considering the arithmetic mean and standard deviation of the moderate and severe covid-19 patients showed in table no.2

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and 4. The pooled standard mean deviation was found 10.91 and the independent sample 't' test was 23.72 respectively.

The significant levels were studied by calculating *'P'* value, when *P<0.00000* was supposed to be highly (extremely) significant. The other statistical parameters like degree of freedom (DF) was 3811, standard error (SE) was 0.46 and 95% confidence interval (CI) was found 10.01 to 11.81. That is showed in table no.2 and 4.

Table no:4 Showing the analysis of 't' value, degree of freedom (DF) and significant levels in moderate and severely affected Covid-19 patients

Sr. No.	Authors and Year	T-test values	Degree of freedom (DF)	Significance levels
1	Alex Pizzini et. al. (2020)	0.12	219	*P<.84 NS*
2	Emilija Atanasovska et. al. (2021)	14.93	64	*P<.0000 HS*
3	Emilija Atanasovska et al. (2021)	33.45	64	*P<.0000 HS*
4	Antonio D. Avolio et al. (2021)	28.06	144	*P<.0000 HS*
5	Antonio D. Avolio et al. (2021)	38.93	146	*P<.0000 HS*
6	Anshul Jain et al., (2020)	19.91	306	*P<.0000 HS*
7	A. Catharine Ross et al.,(2021)	52.22	422	*P<.0000 HS*
8	Mustafa Demir (2021)	139.8	174	*P<.0000 HS*
9	Bagcilar Egitim ve Arastirma Hastanesi et al. (2021)	12.09	135	*P<.0000 HS*
10	Irene Campi et al., (2021)	6.76	153	*P<.0000 HS*
11	Irene Campi et al., (2021)	0.05	153	*P<.9602 NS*
12	Pizzini Aet al (2021)	2.3	107	*P<.0000 HS*
13	Nirav Nimavat et al (2021)	0.52	154	*P<.6 NS*
14	Amiel A. et al (2022)	5.58	85	*P<.0000 HS*
15	Jain et al. (2020)	24.89	162	*P<.0000 HS*
16	Yvette C. Cozier et al., (2021)	59.1	883	*P<.0000 HS*
17	Luigi Gennari et al., (2020)	1.14	101	*P<.2542 NS*
18	Combined estimation	23.72	3811	*P<.000000 VHS*

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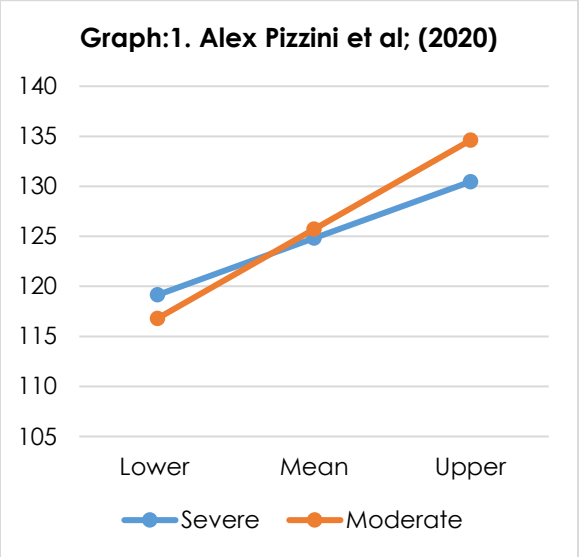
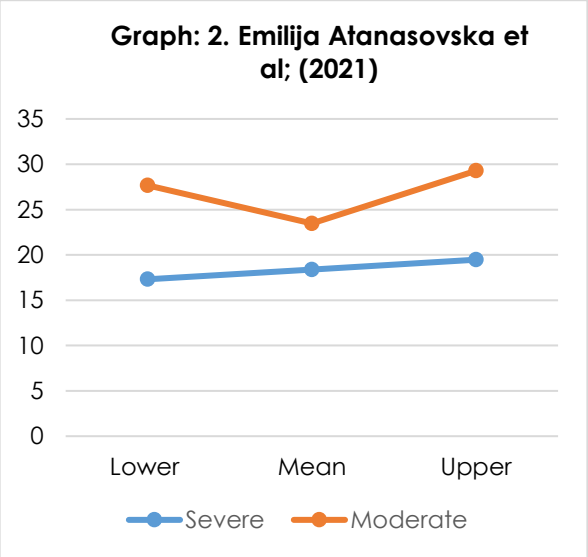
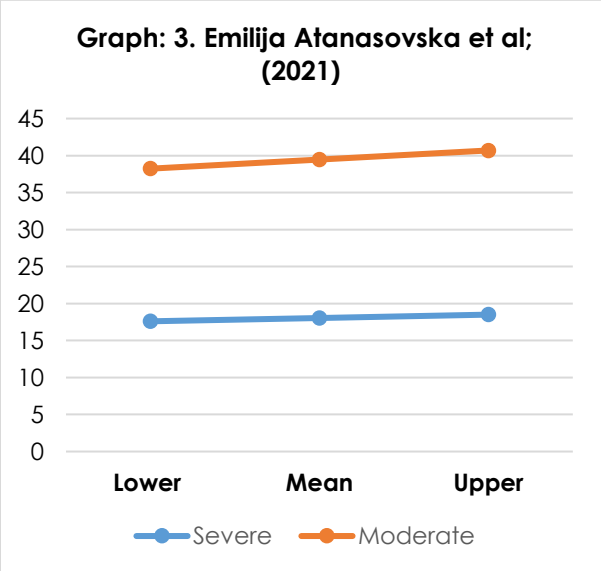
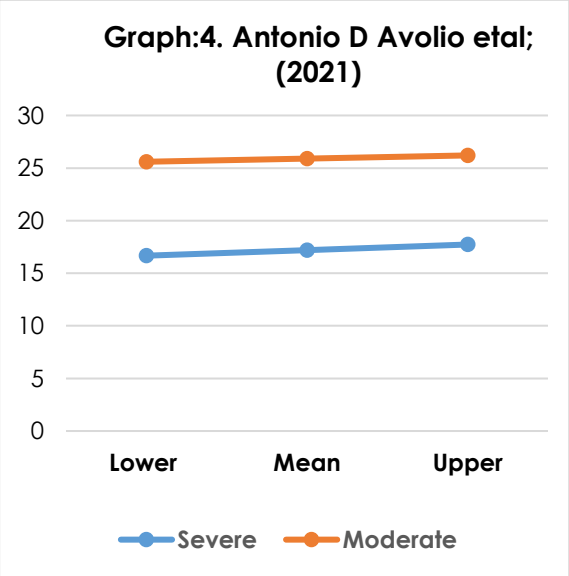
The line graphs of individual articles was drawn by considering means and confidence intervals of each research paper and then considered the combined estimated value of all articles.









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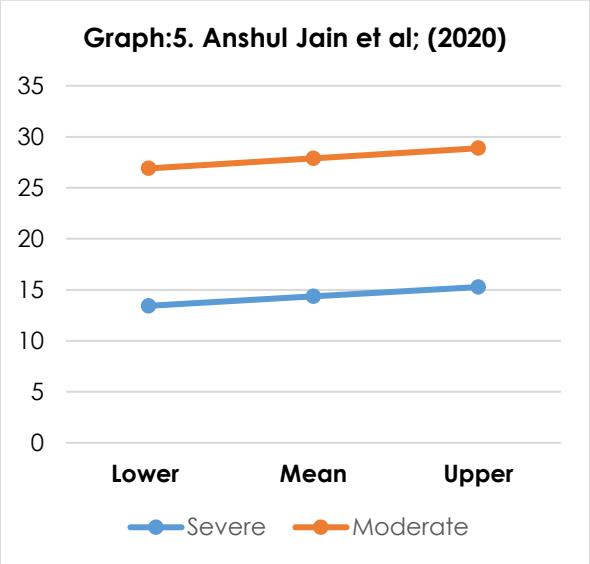

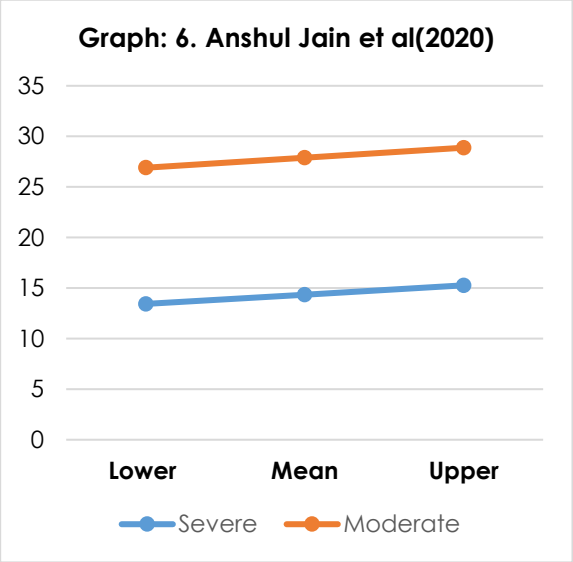

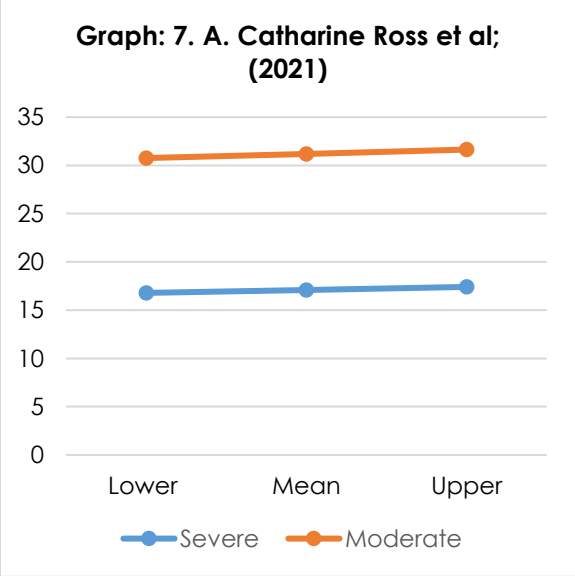

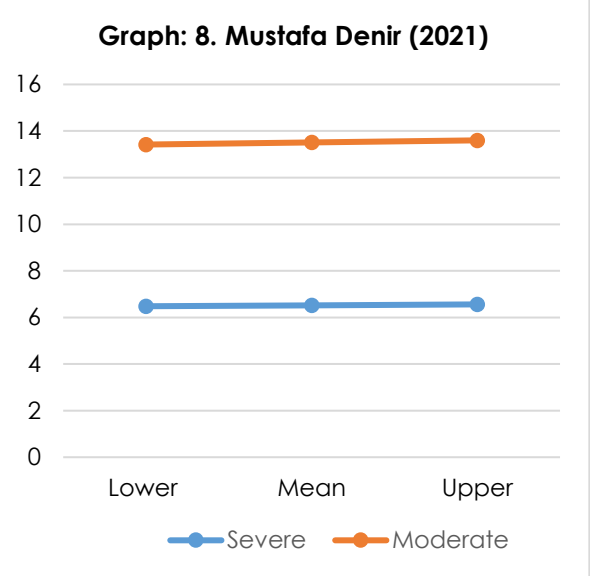

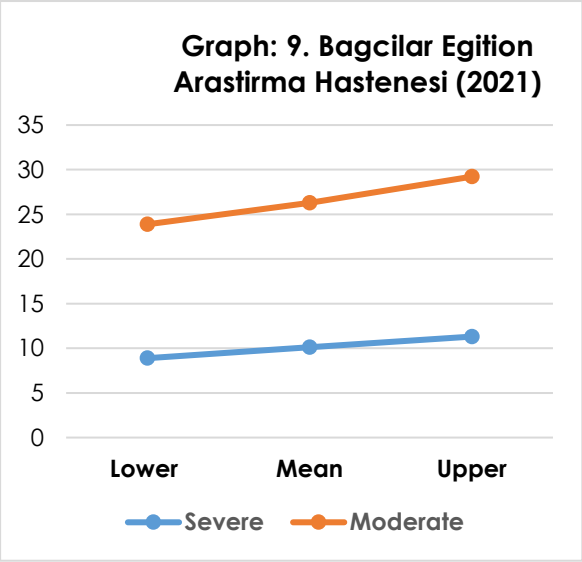

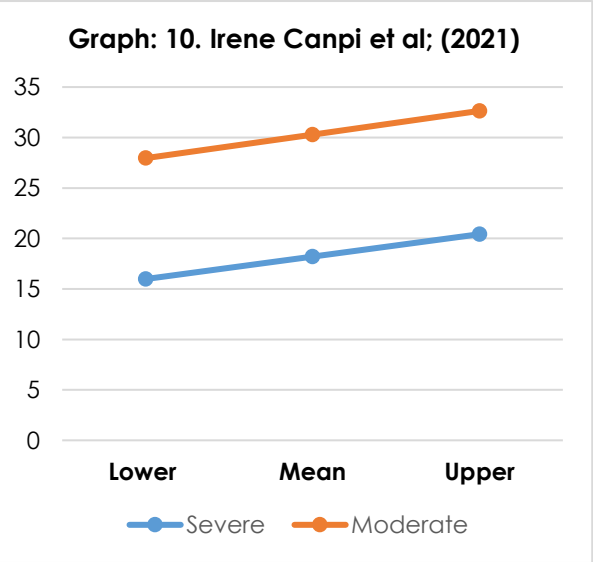

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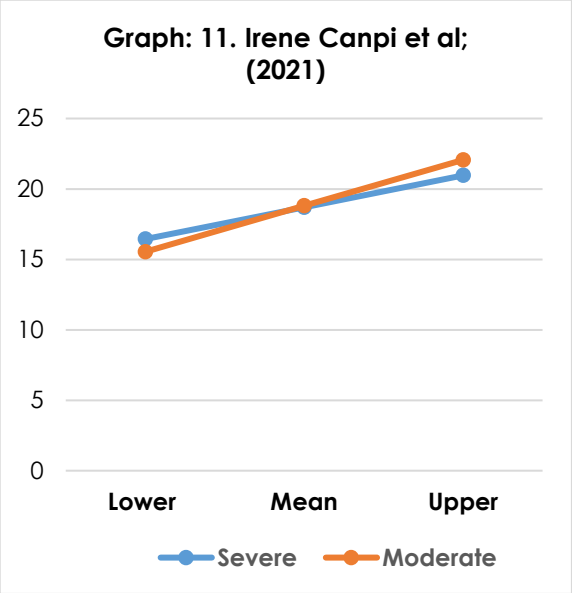

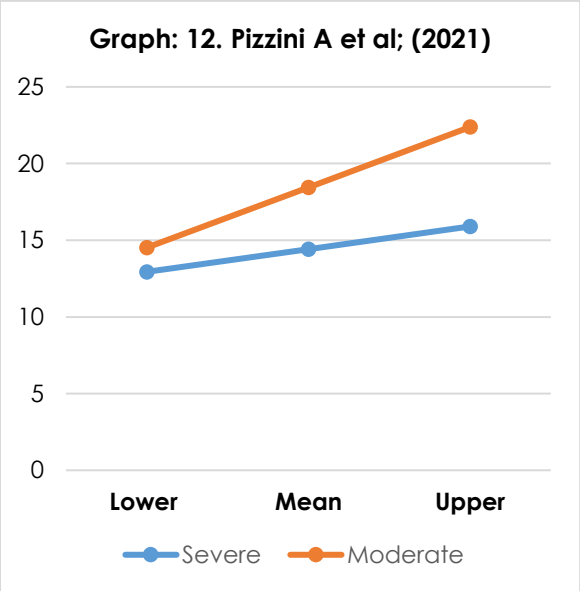

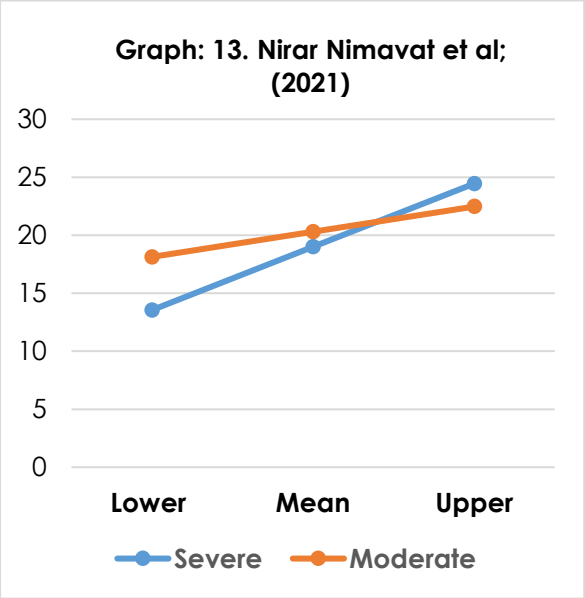

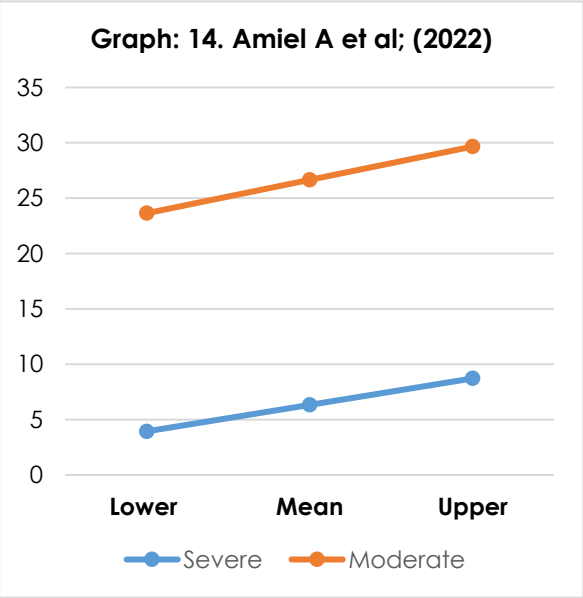

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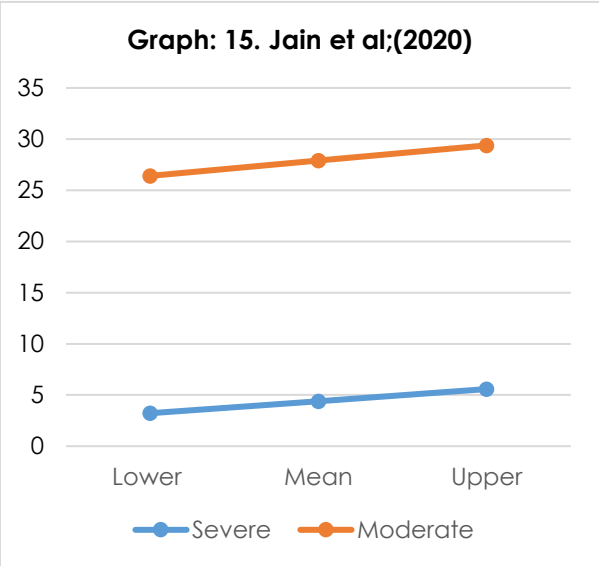

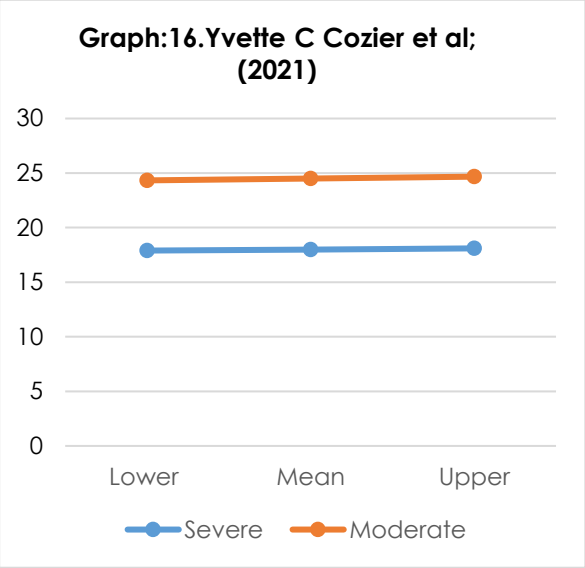

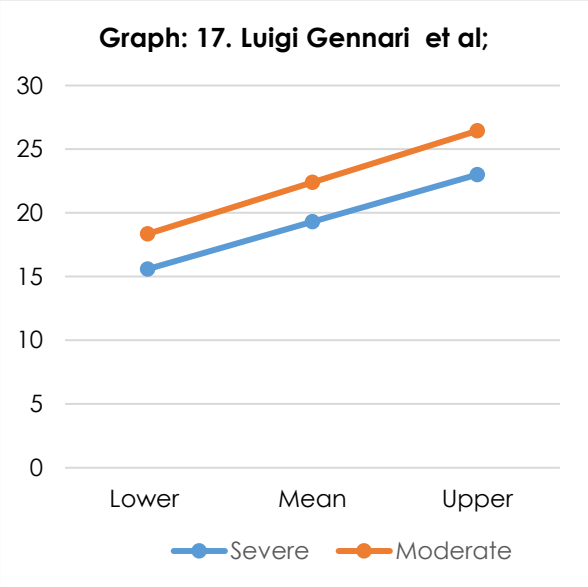

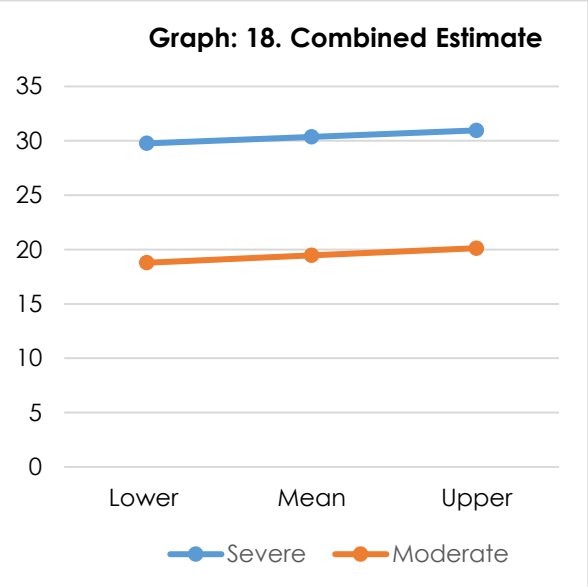

FOREST PLOT (GRAPH-19):

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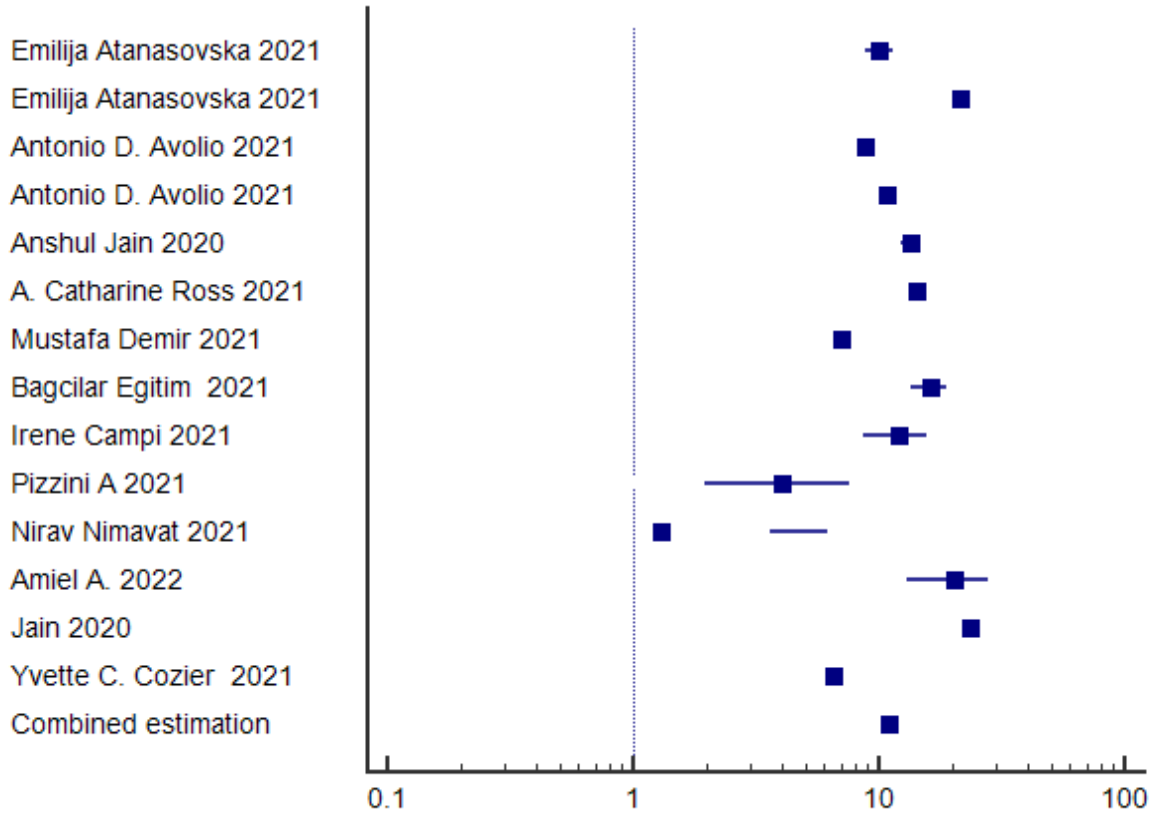

Forest plot (Graph-19) showing different studies with Standardized mean difference with individual confidence intervals. Bottom line shows combined estimate with 95% confidence interval showing a very significant difference.

Since these 3 studies, showing lower limit of confidence interval around the SMD is below zero. These studies were not included in the forest plot, so it is mentioned separately. However, these studies were included in the calculation of the combined estimation.

The table no:5 showing the details of these studies.

Table no: 5

Authors and Year	**SMD**	**LCL**	**UCL**
Alex Pizzini 2020	0.9	-13.7	15.5
Irene Campi 2021	0.1	-3.78	3.98
Luigi Gennari et 2020	3.1	-2.27	8.47

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DISCUSSION

In the first study line diagram of Alex Pizzini et. al. (2020) in graph:1. showed that serum vitamin-25 OH-D levels were found decreased in severely infected covid-19 patients as compared to non significantly increased in moderately infected covid-19 patients. It is supported by Irene Campi et al., (2021) by stating that, there was a significant difference observed for mean 25OH-D levels among severely-symptomatic COVID-19 patients as compared to mildly-symptomatic COVID-19 patients and controls. 25OH-D showed significant lower values in severely symptomatic COVID-19 patients respect to mildly symptomatic COVID-19 patients and to non SARS -CoV- 2 infected controls.[6]

Similarly, Panagiotou G, et. al. in (2020), Hars M,et al. in(2020),Radujkovic A. et al.(2020) De Smet D et al. in(2021), Hernández JL.et al.in (2021),Merzon E, et al.in(2020), and Maghbooli Z et al.in (2020) also reported that, the plasma 25OH-D levels were decreased in hospitalized, severely affected COVID-19 patients that in the mildly-symptomatic COVID-19 patients and in non SARS-CoV-2 infected controls. These data confirm and demonstrate with previous articles that, vitamin D deficiency is associated with the clinical outcomes of COVID-19. [7-13]

Emilija Atanasovska et. al. (2021) in graph:2 and Antonio D. Avolio et al. (2021) in graph:3 were observed the lowering state of 25OH-D in their line graphs so they were potentially suggested that, 25OH-D levels were significantly lowered in severely infected patients COVID-19 patients and in acute respiratory distress syndrome (ARDS). [14-15]

Alipio M. in 1919, he conducted the retrospective observational studies in South Asian 212 patients of covid-19 (mild-78 nmol/L, ordinary-68.5 nmol/L, severe-53 nmol/L and critical cases *(P< .001)* he found that, there was a significant decrease of Sr. 25 OH-D levels in covid-19 infected patients. [16]

Anshul Jain et al.,(2020) were reported that, Sr. 25 OH-D levels in severely infected patients were (highly) significantly decreased as compared to the moderately infected covid-19 patients, since the 't' test was 19.91; DF was 306 and *P< .0000* HS.

The line graphs: 5&6 showed significant difference in Sr. 25 OH-D levels in between moderate and severe covid-19 patients. This study could be supported by Macaya F. et al.,stating that vitamin D deficiency tended to predict the increased susceptibility for developing severe COVID-19,cardiac disease and renal disease.[17] Carpagnano GE et al.,studied that the patients with severe deficiency of vitamin D had the significant higher mortality rate.[18]

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A. Catharine Ross et al.,(2021) studied Sr. 25 OH-D levels on 212 covid -19 patients (mild 100 + severe 112), the results were 't' test was 52.22, DF was 422 and significance level *P<0.0000* was found highly significant indicating that,(in graph:7) Sr. 25 OH-D levels were significantly decreased in moderate patients and severely in sever covid-19 patients. The similar findings were observed by: Panagiotou G et al., (2020)[19] Hars M, et al., (2020),[20] Radujkovic A. et al., (2020)[21] De Smet D et al., (2021),[22] Hernández JL, et.al., 2021,[23] Merzon E.et al., (2020),[24] and Maghbooli Z.et al (2020). They stated that, the circulating 25OH-D levels were significantly decreased in covid-19 patients and predicted the same in the patients of respiratory distress syndrome.[25]

Mustafa Demir et al.,(2021) studied on 176 (80 + 96) patients, the line graph: 8 of the study indicated that, sr. 25OH-D levels are decreased in moderate and severely decreased in covid-19 patients, so two lines are (differ) apart from each other. [26] Therefore, the researchers suggested that, sr.25 OH-D level may be have the potential therapeutic approach to covid-19, and it is more likely have also protective effects against covid-19, it might be related to the suppression of cytokines response, it seems possible that, the appropriate dose of 25 OH-D may decrease the severity of illness caused by covid-19 patients.[27,28,29]

Bagcilar Egitim ve Arastirma Hastanesi et al. (2021) found that, there was a significant different in Sr. 25OH-D levels in moderate and severely affected covid -19 patients. They conducted the study on total 137 (34 severe and 103 moderately) affected patients and they found the calculated 't'=12.09, df =135; and *P<. 0000* was highly significant. The line graph: 9 showed that the Sr. 25OH-D levels in severely affected covid -19 patients is significantly lowered as compared to moderately affected patients.[30]

Irene Campi et al., (2021) studied on 52 moderate and 103 severely affected patients and then reported that, there was a highly significance difference in moderate and severely affected covid -19 patients since the . *P< .0000,* The in line graph: 10 showed significant difference. However in second study of Irene Campi et al., (2021) the mean and standard deviation was not varies in both the groups [(18.8 (11.7):18.7 (11.6)] so the second graph is closely intersecting and the calculated value of P < *.9602* so, in line graph: 11, showed overlapping line since, there were no significance difference in both moderate and severely affected covid-19 patients.[6]

Pizzini A.et al (2021) studied that, sr. vitamin-D level was showed significant variations in between severely and moderately affected covid-19 patients, the graphical presentation 12, also

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showed the highly significant difference between moderate and severely affected covid-19 patients.[31] Nirav Nimavat et al (2021) after studying on (156 + 204) optimal mild to moderate and severe covid -19 patients, they reported that, the serum calcitriol levels were showed statistically significant difference in between optimal to mild moderate and severe covid-19 patients, But the line graph:13 were found intersecting with each other's. [32]

J.J. Cannell, R. Vieth, J.C. Umhau, et al; (2006) stated that, Vitamin D is very important for inducing human immune system by decreasing the viral infection incidences coinside with epidemic of influenza it might be due to its ultraviolet radiation effect and vitamin-D, so called as 'seasonal stimulus' [33]

Amiel A. et al (2022) in their retrospective study, with their multivariable analysis they noted that, serum 25(OH)D level was found to be positively correlated with COVID- 19 illness severity. The comparison between pre-infection calcitriol values and Covid-19 disease severity demonstrated that, there was a progressive decrease in 25(OH) D levels as the severity of disease increases, so the line graph:14. showed significant variation running apart from each other. They found the significance difference in between moderate and sever covid-19 patients was increased with decreased in serum 25(OH) D levels by 86%. [34] Similarly, Kara M,et al., (2020) supported our various articles stating that, the hospitalized COVID-19 patients have been shown to present lower mean and median levels of 25(OH)D3 than the normal healthy population and COVID-19 OPD.[35]

Jain et al. (2020) through the meta-analysis study they are stating through line graph:15. that, vitamin D is deficient in Covid-19 patients, they studied on 154 covid-19 patients making the two groups 91 (asymptomatic) and 63 (severe/ critical covid-19) patients the asymptomatic group showed 31.86% and critical showed 96.82% calcitriol deficiency. The Chi square test difference in the prevalence of calcitriol among two groups was found to be highly significant. So, 154 patients, 90 patients were found to be deficient in vitamin D among which 61 were critical and 29 were asymptomatic. These two articles were supported by Macaya F, et al., (2020)and Carpagnano GE et al., (2021).[17, 18]

Yvette C. Cozier et al., (2021) In our meta-analysis study it was found that, serum calcitriol level was very low in moderately infected covid-19 patients since the statistical SMD value was 6.5; df= 883; calculate 't'=59.1 and $P < .00000$ showed highly significant and line graph 16 also showed variations. This showed that, there was increased covid-19 infections found in decreased serum 25(OH) D levels.[36]

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In similar studies like, Kaufman HW et al (2020), D'Avolio A, Avataneo V et al. (2020), Meltzer DO,et al.(2020), Ilie PC et al., (2020), and Hastie CE, et al., (2020) noted that, several recent studies have studied and observed that the role of vitamin D levels in relation to COVID-19 infection, with in consistent results with decreased vitamin D [37, 15, 38-40]. An increased in the possibilities of infections in those with lower 25(OH)D levels, the recorded data from UK Biobank indicated similar 25(OH)D levels among those who tested positive to COVID-19. The largest U.S. study, based results from a national laboratory, provides the strongest evidences of the association between declined 25(OH)D level that induces in increased risk of COVID-19 in U.S. populations.[40]

Luigi Gennari et al., (2020) reported (graph : 17) that, the serum calcitriol is found decreased in covid-19 infected patients (103 = 51 mild + 52 moderate) with respiratory distress syndrome but their statistical study showed non-significant since calculated SMD= 3.1 and *P<0.2542.* They also reported that, supplementation of vitamin-D could be helpful in the treatment of RDS and Covid- 19 patients.[41]

Combined estimation: Combined estimation of meta-analysis study of serum 25(OH) D levels (total: 2673 = 1316 moderate + 1297 severe) in COVID-19 patients through seventeen studies showed that there were statistical very highly significant variations was observed in in (graph: 18) the mild and moderately affected covid-19 patients stating that, the serum 25(OH) D levels was found severely declined as the severity of covid-19 infection increased. The combined study will help to make the decision and conclude the topic of meta-analysis.

Schwalfenberg GK et al., (2011),Liu PT, et al., (2006), Adams JS,et al., (2009) and Laaksi I.et al., (2012) reported that, the adequate concentration of serum 25(OH)D in human body will induce innate cellular immunity and strengthened by the action of vitamin D and also with the induction of antimicrobial peptides including the human cathelicidin LL-37. [42-45]

Forest plot: Graph-19: showed different studies with Standardized mean difference with individual confidence intervals.

The combined estimation with 95% confidence interval also showed a very significant difference. The 3 studies (1,13 &17) mentioned showing lower limit of confidence interval around the SMD is below zero. However, these studies were included in the calculation of the combined estimation.

CONCLUSION

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In the mea- analysis study we found that, there was an inverse association between serum calcitriol 25(OH)D and the severity of SARS Covid-19 infection conditions. As the vitamin D deficiency markedly increases the severety of Covid-19 infections also increases.

LIMITATIONS: The study is retrospective laying on the statistical data, different observations and conclusions of the past published studies. We have studied only one variable serum calcitriol 25(OH)D level in moderate and severe covid-19.

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