Vitamin D , a predictor of outcome in COVID-19 patients

Abstract

Introduction:

Low vitamin D is a very common associated with more probability of pulmonary infections. Present days, are the days of pandemic of the Coronavirus disease 19 (COVID 19). Fatality associated with this disease is because of some sort of immune dysfunction like a cytokine storm. Many studies proved role of vitamin D in proper functioning of the immune system. But other did not have any correlation with disease severity due COVID 19 , In this situation of grave COVID-19 pandemic , studies on vitamin D for COVID-19 are immensely needed as no specific antiviral available for COVID-19 at present. Hence this study was undertaken to find out relation of vitamin D levels and outcome due to COVID-19.

Methods:

This is a single centre case control study. 250 study participants included in the study suffering from COVID-19, treated in Acharya Vinobha Bhave rural hospital (AVBRH), a tertiary care centre. It was a case control study at Acharya vinoba bhave rural hospital of central India, a tertiary care centre.Study design was case control retrospective observational analytical.Study population was hospital base cases and controls with clear Definition of cases, controls , inclusion, exlusion criteria, outcome and exposure. Statistical analysis was done to measure the association of outcome (the death or severe disease risk) with exposure (low vitamin D) and that was determined by measuring Odds ratio . The study was approved by the Institutional ethics committee of university.

Results

Most of the patients (45%) were in an age ranging from 40 to 59 years . Maximum number of the patients (68%) have one comorbidity. Diabetes mellitus and hypertension , both present in 28 % and other co morbidity in 40 % of patients and 32% of patient reported to have no co morbidity.

Present study reveals vitamin D deficiency in in around 74% of patients. Most of the patients were managed without supplementation of oxygen, but few needed high flow oxygen and even invasive ventilation. Fortunately over all prognosis was good. Death was in only 2% of cases. all died patient and patient with severe disease had vitamin D deficiency. This association of hypovitaminosis D was more significant than other co morbidities including hypertension and diabetes mellitus.

Conclusions

In around two third of patients were having vitamin D deficiency. Study clearly depicts severe vitamin D deficiency is associated with deaths. Hence it can be used as a predictor of mortality.

Keywords – Poor prognosis, pan endemic, respiratory disease, cytokine storm

Introduction

Disorders due to low vitamin D level are also a pandemic, affecting paediatric and geriatric population. Several investigators are agreed upon connection in between vitamin D deficiency and disturbed immune system predisposing severe respiratory tract infections. It was observed further that there is an association in between critically serious patients and vitamin D

deficiency with bad outcomes like even death[1]. Vitamin D is not found in a human dietary source. It is synthesised by human skin and liver in a presence of sunlight. Along with its important role in bone health, as increasing intestinal assimilation of calcium and phosphorus , it has very important action to boost human immune system[2].

Coronavirus disease 19 (COVID-19) is primarily attacks a respiratory tract with mild to severe clinical presentation including even death. The pathophysiology of this exorbitant fluctuation in clinical presentation is exactly corelated with the cytokine storm. This abnormal cytokine storm is due to underline deficient immune system. Number of studies highlighted role of vitamin D as immune booster[3,4].

Many researches proved positive association of vitamin D and COVID-19 outcomes , while other studies did not prove it[5,6]. For example Ali et al[7] suggested not sufficient proof on the correlation between vitamin D levels and COVID-19 severity and deaths. Furthermore, there is less evidence on the correlation between vitamin D levels and COVID-19 deaths . In this situation of grave COVID-19 pandemic , studies on vitamin D for COVID-19 are immensely needed as no specific antiviral available for COVID-19 at present. Therefore, this study was undertaken to evaluate the possible correlation between vitamin D levels and disease severity including mortality in COVID 19 patients.

Materials and Methods

Study design-

Case control study,

Retrospective observational analytical

Study population –

Inclusion criteria

Cases and control as per standard definitions given below, selected from patients admitted in Acharya Vinoba Bhave rural hospital (AVBRH) Wardha from September 2020 up to October, 2020. We included incident cases means newly occurring cases to reduce bias. Hospital based cases and control were selected with anticipating error of getting more severe cases than population.

Exclusion criteria

Previously known and treated patients of Vitamin D deficiency

Prevalent cases to reduce bias

Definition of cases and controls

In present study patients with severe disease with or without death are considered as cases and patient with mild disease or without symptoms considered as controls. patients needed oxygen supplement or ventilatory support or with circulatory event were categorised as severe disease. Patients managed without oxygen or without circulatory event were considered as mild disease.

Identification COVID-19 cases were as per guidelines of world health organisation(WHO)[1] with a positive result on real-time reverse transcriptase-polymerase P chain reaction (RT-PCR) assay from nasal and pharyngeal swab specimens.

Definition of outcome

Severe disease(as per definition mention above) with or without death considered as outcome

Definition of exposure

Serum vitamin D levels more than 30ng/ml considered as normal and less than 30ng/ml as deficiency (further categorised into mild, moderate and severe 20–29, 10–19, and <10 ng/mL, respectively)[1].

Sample size -250

Data collection

A patient both cases and control selected were having positive result on real-time reverse transcriptase-polymerase P chain reaction (RT-PCR) assay for COVID 19 from nasal and pharyngeal swab specimens. Cases and controls selected independent of vitamin D status that is a exposure in this study, Data was retrieved from the medical records of 250 admitted patients in Acharya Vinoba Bhave rural hospital (AVBRH) Wardha from September 2020 up to October, 2020 and it was collected by first Author.

Sample size- 250 Participants included

Statistical analysis.

Data entry mode was manual. Analysis of data was calculated to measure the association of outcome (the death or severe disease risk) with exposure (low vitamin D) and that was determined by measuring Odds ratio .

Project implementation plan (quality assurances)

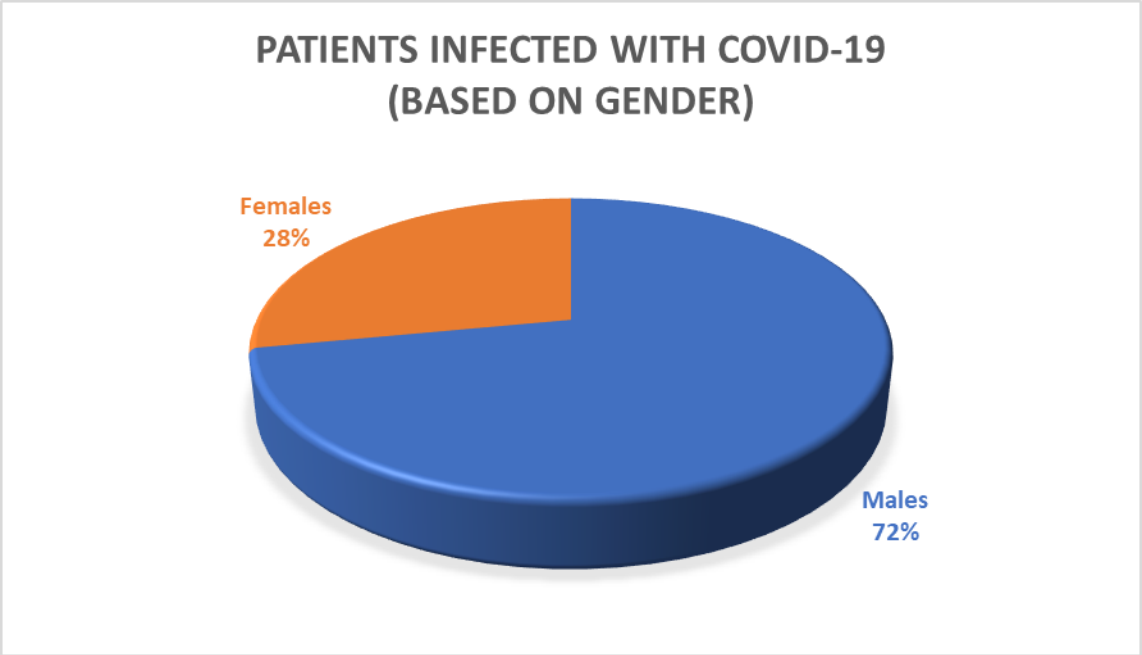
Data was collected objectively assuring reproducibility, accuracy and precision in exposure measurement, as it was from standard laboratory and performed by principal investigator .

Human subject protection

The study was approved by the Institutional ethics committee of university. (Ethical Committee number: DMIMS(DU)/IEC/2020-21/9128). Confidentiality of data was maintained.

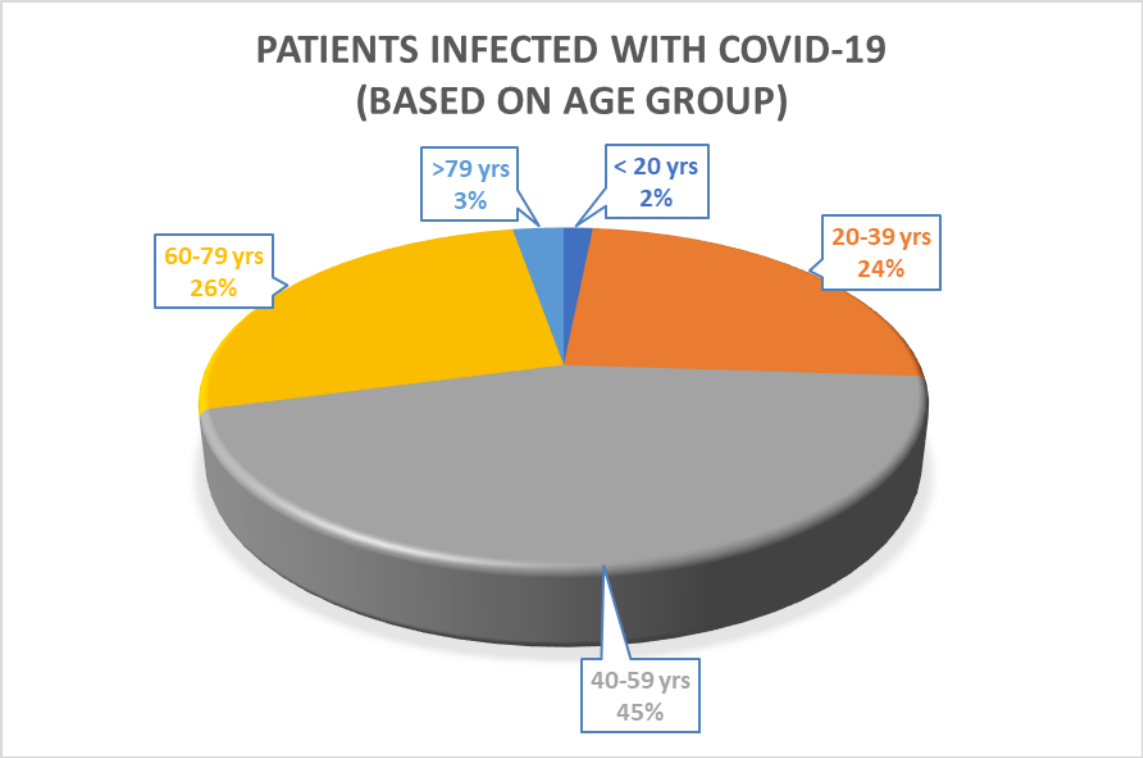
Results

Graph 1 Gender distribution



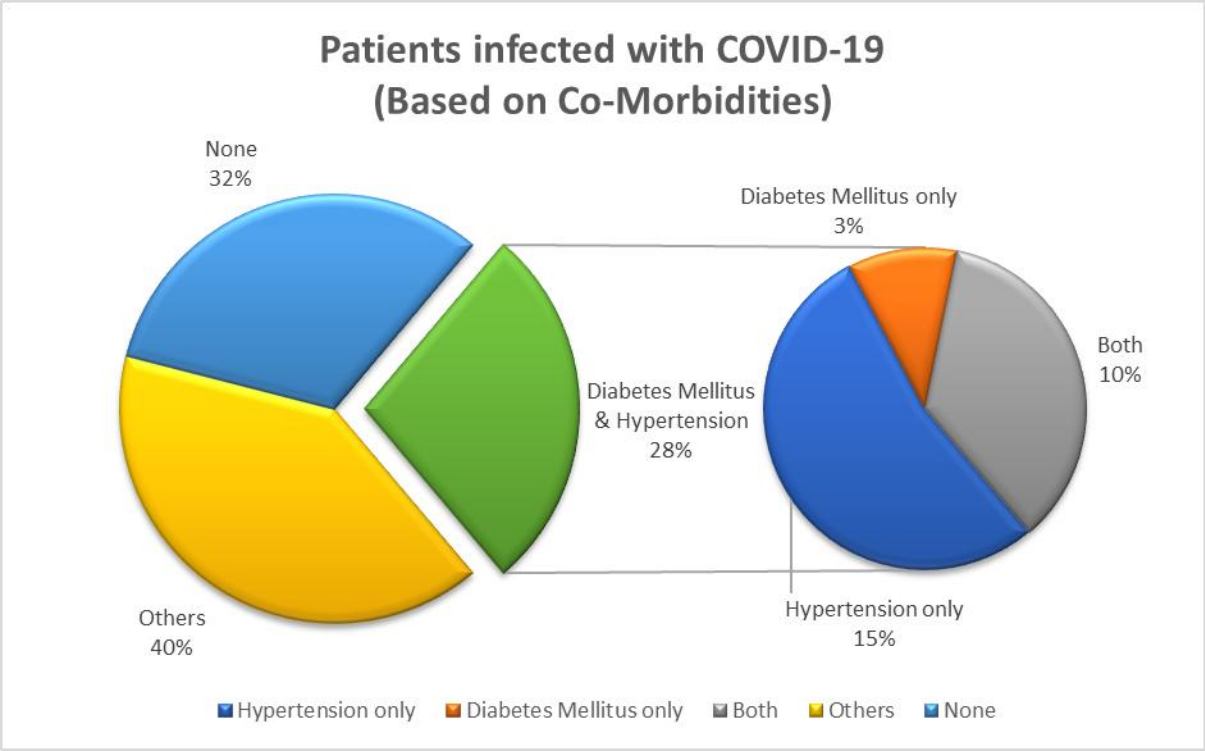
250 patients included in study. Males were outnumbered than women (72% vs 28%).

Graph 2 Age distribution



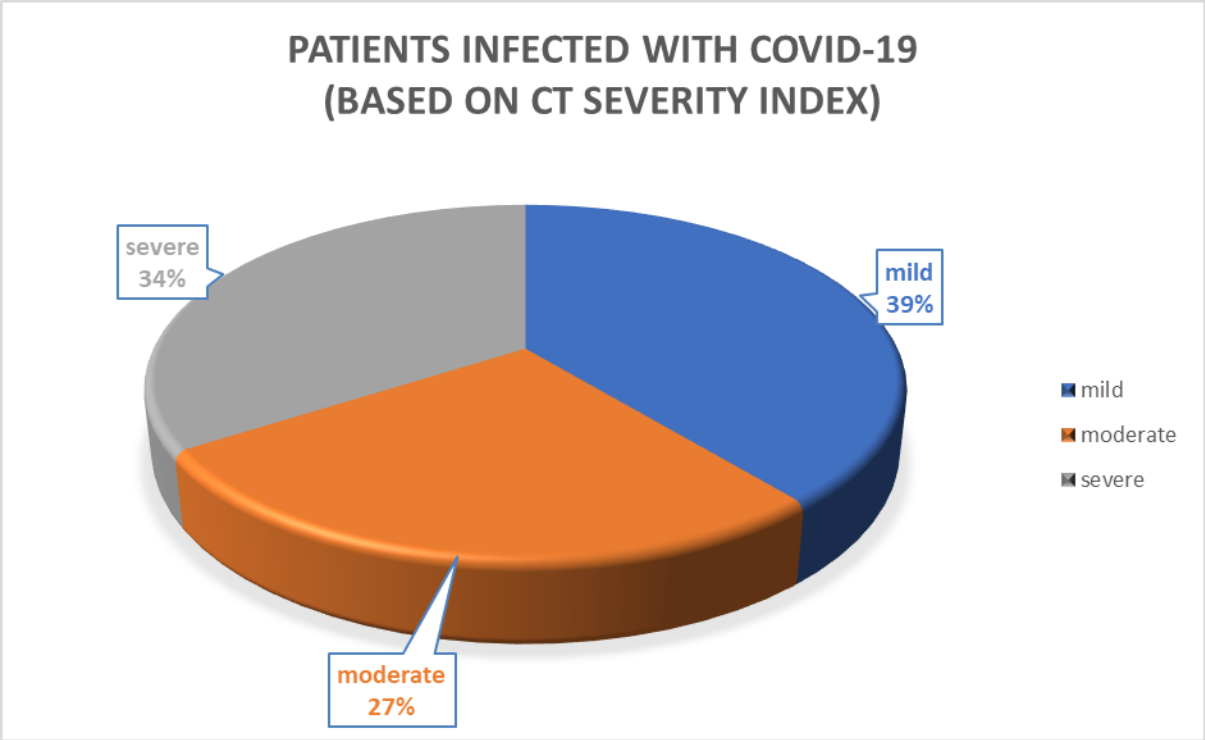
Most of the patients (45%) were in a 40-59 years age range and least in age less than 20.

Graph 3 Co-morbidities' distribution



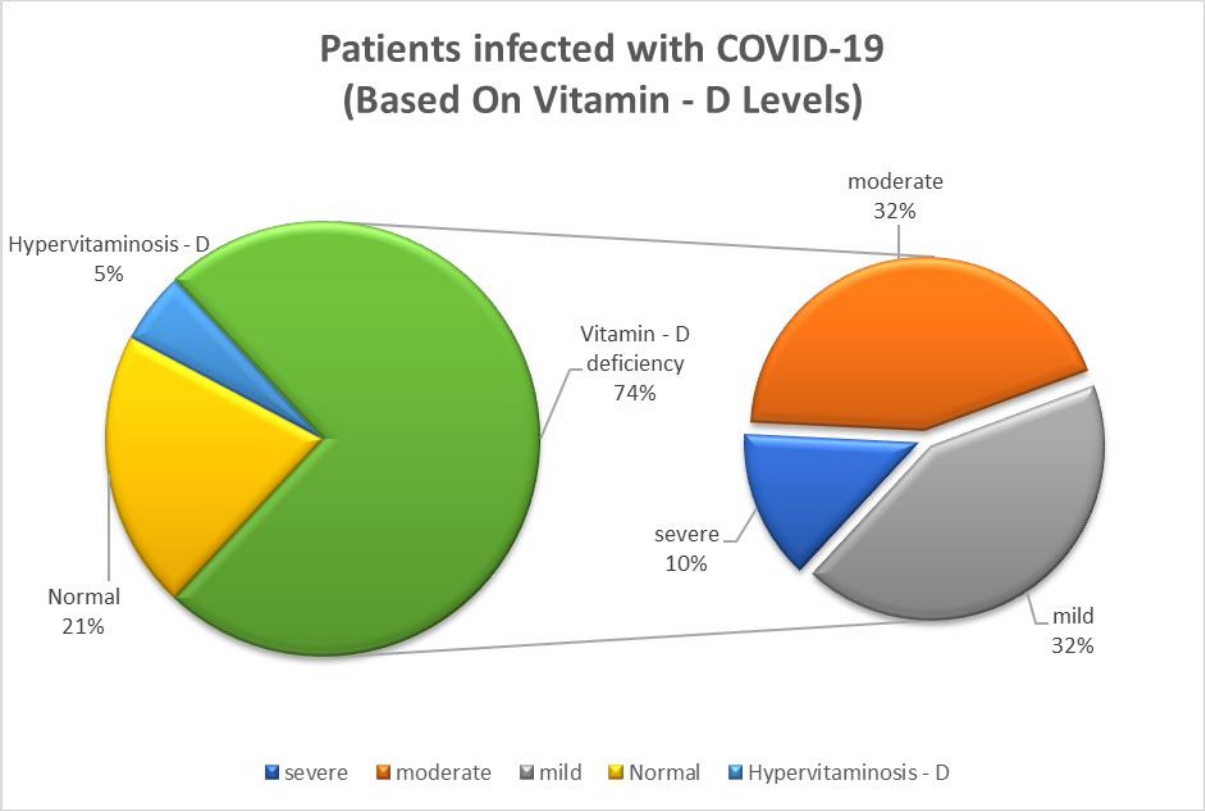
(68%) participants have single associated disease as a comorbidity. 32% of patient reported to have no co morbidity.

Graph 4 Computerized tomography (CT) severity index



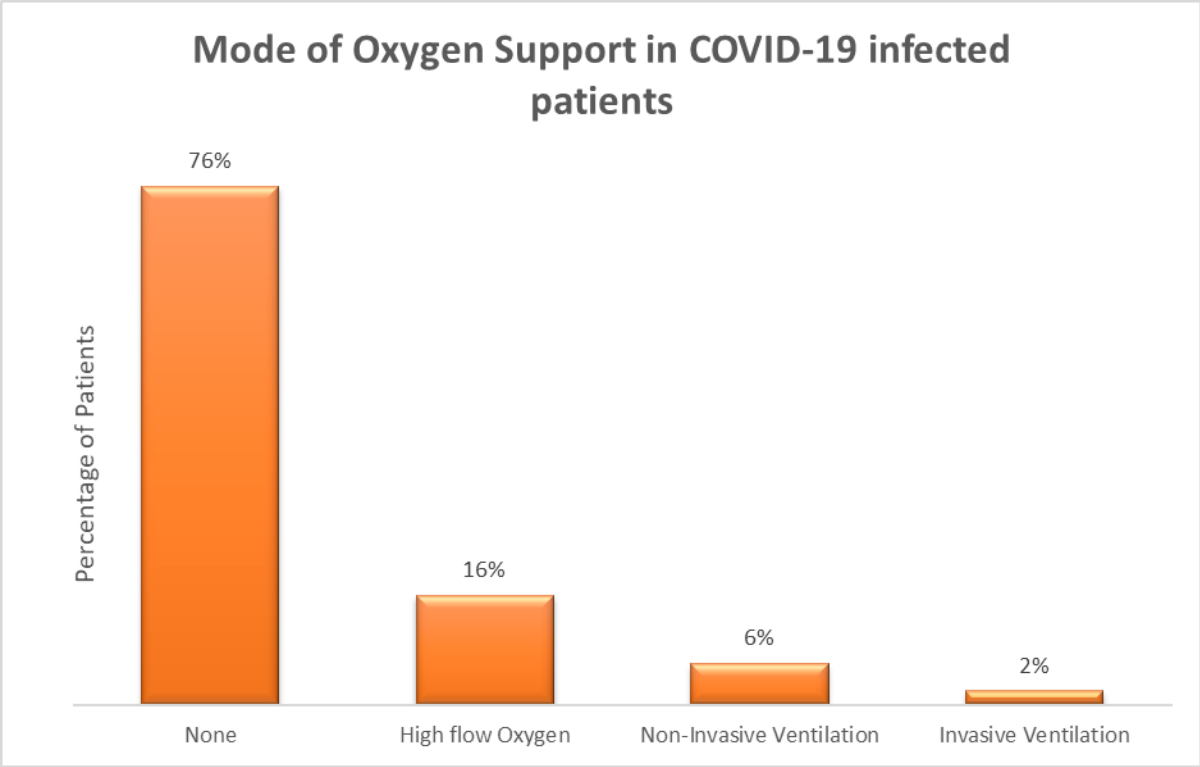
As per CT severity index 34 percent have severe disease,27% have moderate disease and 39% have mild disease.

Graph 5 Patients infected with COVID-19 based on vitamin D levels



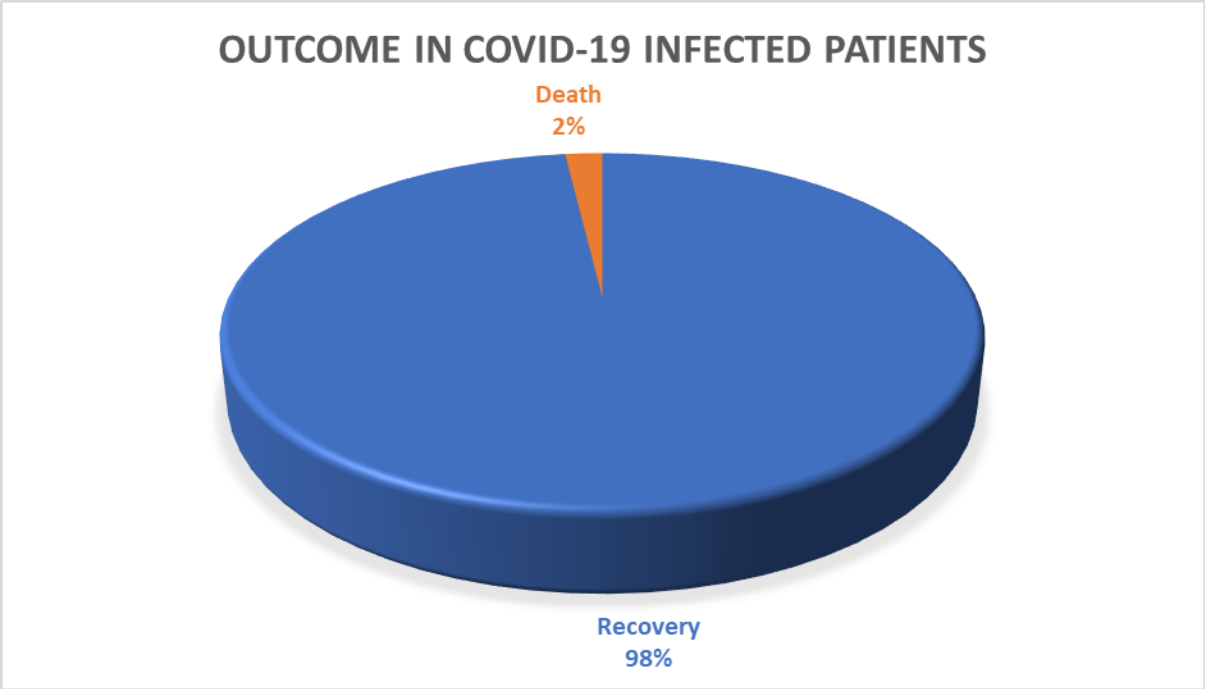
In around two third of patients were having vitamin D deficiency(74%). 10% had severe deficiency and mild and moderate deficiency in 32% each, 21% shows normal levels and 5% subjects shows hypervitaminosis D.

Graph 6 Mode of oxygen requirements in a treatment of COVID-19 patients



Most of the patients (76%) were managed without supplementation of oxygen ,16% patients required high flow oxygen,6 % needed non-invasive ventilation and 2% patients have invasive ventilation.

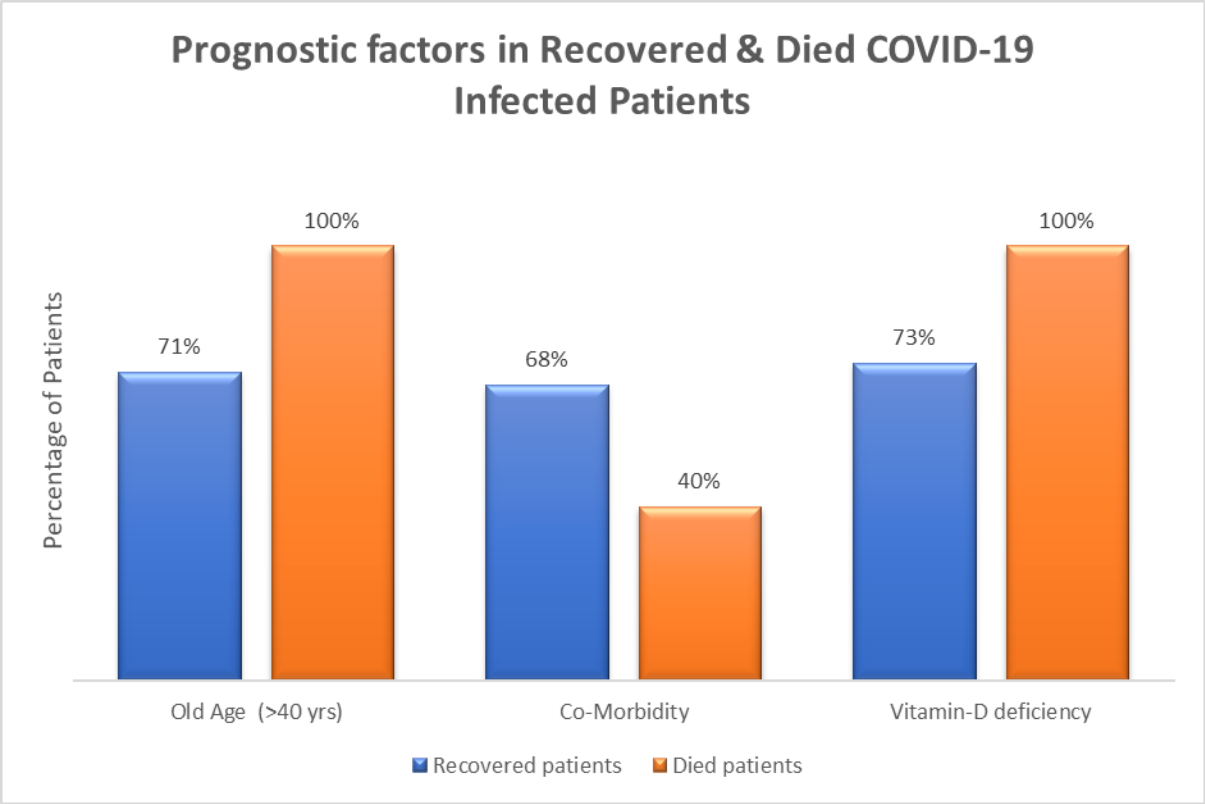
Graph 7 outcome in COVID-19 patients



Above graph depicts that 98% patients recovered fully, death was in only 2% of cases.

All 5 fatalities were having severe vitamin deficiency having levels of vitamin D less than 10 ng/ml.

Graph 8 Assessment of prognostic factors



Above figure shows that in all died patient have severe vitamin D deficiency and age more than 40 years and this association of hypovitaminosis D was more significant than other co morbidities including hypertension and diabetes mellitus.

Table 1 shows association vitamin D deficiency and mortality

	Death	survived	Total
Hypovitaminosis D	5 (a)	180 (b)	185(a+b)
Normal or hypervitaminosis	0 (c)	65 (d)	65 (c+d)
	(a+c)	(b+d)	(a+b+c+d) 250

odds ratio =1.80

as odds ratio is more than 1 hence hypovitaminosis is positively associated with death.

Table 2 shows association vitamin D deficiency and disease severity.

	Severe disease plus death	Asymptomatic or mild disease
Hypovitaminosis D	49	136
Normal or hypervitaminosis	11	54

Odds ratio =1.76

as odds ratio is more than 1 hence hypovitaminosis is positively associated with severe disease or death.

Discussion

This was an analytical single centre case control study. It comments on the link in between vitamin D serum level and fatality of COVID19. Males were outnumbered than women (72% vs 28%). (see graph 1)Most of the patients (45%) were in an age group of 40-59 years followed by the age group of 60-79 years of around 26%. (see graph 2)

Most of the patients (68%) presented at least one comorbidity. hypertension and Diabetes mellitus both present in 28 % and other co morbidity in 40 % of patients and 32% of patient reported to have no co morbidity. (see graph 3)As per CT severity index 34 percent have severe disease,27% have moderate disease and 39% have mild disease. (see graph 4)

In around two third of patients were having vitamin D deficiency(74%). 10% had severe deficiency and mild and moderate deficiency in 32% each, 21% shows normal levels and 5% subjects shows hypervitaminosis D. (see graph 5) Most of the patients (76%) were managed without supplementation of oxygen ,16% patients required high flow oxygen,6 % needed non-invasive ventilation and 2% patients have invasive ventilation. (see graph 6) Fortunately over all prognosis was good.98% patients recovered fully, death was in only 2% of cases. (see graph 7) all died patient have severe vitamin D deficiency and age more than 40 years and this association of hypovitaminosis D was more significant than other co morbidities including hypertension and diabetes mellitus. (see graph 8) After calculating Odds ratio it was concluded that hypovitaminosis D was associated with bad prognosis in COVID 19patients like mortality and severe disease. (see table 1 and 2)

Giovanna Elisiana Carpagnano et al [1] conducted similar study and obtained results depending on vitamin D serum levels one fifth of patients had normal vitamin D levels, one fourth had mild deficiency, rest have moderate and severe deficiency, Giovanna Elisiana Carpagnano et al[1] also suggested similar findings in their study and proves a strong association of vit D deficiency and bad prognosis in COVID 19 patients. results are comparable to present study.

Dancer RC et al[3] conducted study reveals that vitamin D deficiency association is present who develop acute respiratory distress syndrome (ARDS). This hypovitaminosis supposed to help in creating body environment possibly because of deficient immunity susceptible to ARDS.

Grant WB et al[4,] his article explains that prescription of vitamin D can lower the chance of pulmonary infections and subsequent consequences like ARDS and even deaths in COVID 19 patients.

Petre Cristian Ilie et al[5] suggested that severe low vitamin D level is responsible for mortality in aging population of European countries. Lehouck et al[6] also explained effect of administration of high doses of vitamin D in decreasing disease severity and prognosis of chronic obstructive pulmonary disease (COPD). Also depicts the severe vitamin D deficiency can alter the prognosis.

Although Ali et al[7] suggested no correlation between vitamin D levels and COVID-19 severity and deaths but they put forth evidence showing protective effect of vitamin D supplementation against pulmonary infections.

Xu Y et al[8] advocated to administer vitamin D to halt disease progression of COVID-19 patients by boosting immunity.

Whittemore PB et al[9] suggested in his outcome of research that deaths due COVID 19 in a country near to the equator are less than those that away from it. He postulated probably it is an effect of ultraviolet radiation of sunlight is more near the equator which increases vitamin D deficiency. Hence obviously farther places from equator have vitamin D deficiency. More COVID-19 death may be due to less sun exposure.

Conclusions

In around two third of patients were having vitamin D deficiency. Study clearly depicts vitamin D deficiency is associated with deaths and severe disease manifestations. Hence it can be used as a predictor of mortality.

Recommendations

A universal guideline must develop to treat vitamin D deficiency in patients of COVID 19 .

Limitations

As the sample size is small hence it is recommended to conduct large multicentred randomised controlled trial including large sample size.

References

1. Giovanna Elisiana Carpagnano, Valentina Di Lecce, Vitaliano Nicola Quaranta, Annapaola Zito, Enrico Buonamico, Elena Capozza, et al. Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. J Endocrinol Invest (2020). https://doi.org/10.1007/s40618-020-01370-x

2. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord. 2017 Jun;18(2):153-165. doi: 10.1007/s11154-017-9424-1. PMID: 28516265.
3. Dancer RC, Parekh D, Lax S, D'Souza V, Zheng S, Bassford CR, Park D, Bartis DG, Mahida R, Turner AM, Sapey E, Wei W, Naidu B, Stewart PM, Fraser WD, Christopher KB, Cooper MS, Gao F, Sansom DM, Martineau AR, Perkins GD, Thickett DR. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). Thorax. 2015 Jul;70(7):617-24. doi: 10.1136/thoraxjnl-2014-206680. Epub 2015 Apr 22. PMID: 25903964; PMCID: PMC4484044.
4. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020 Apr 2;12(4):988. doi: 10.3390/nu12040988. PMID: 32252338; PMCID: PMC7231123.
5. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res. 2020 Jul;32(7):1195-1198. doi: 10.1007/s40520-020-01570-8. Epub 2020 May 6. PMID: 32377965; PMCID: PMC7202265.
6. Lehouck A, Mathieu C, Carremans C, Baeke F, Verhaegen J, Van Eldere J, Decallonne B, Bouillon R, Decramer M, Janssens W. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2012 Jan 17;156(2):105-14. doi: 10.7326/0003-4819-156-2-201201170-00004. PMID: 22250141.

7. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. J Infect Public Health. 2020 Oct;13(10):1373-1380. doi: 10.1016/j.jiph.2020.06.021. Epub 2020 Jun 20. PMID: 32605780; PMCID: PMC7305922.
8. Xu Y, Baylink DJ, Chen CS, Reeves ME, Xiao J, Lacy C, Lau E, Cao H. The importance of vitamin d metabolism as a potential prophylactic, immunoregulatory and neuroprotective treatment for COVID-19. J Transl Med. 2020 Aug 26;18(1):322. doi: 10.1186/s12967-020-02488-5. PMID: 32847594; PMCID: PMC7447609.
9. Whittemore PB. COVID-19 fatalities, latitude, sunlight, and vitamin D. Am J Infect Control. 2020 Sep;48(9):1042-1044. doi: 10.1016/j.ajic.2020.06.193. Epub 2020 Jun 26. PMID: 32599103; PMCID: PMC7319635. A significant correlation was found between latitude and COVID-19 fatalities.