Is suboptimal circulating level of vitamin D a risk factor for the poor prognosis of COVID- 19? – A comparison of first and second waves in India

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Abstract

Background

- Severe acute respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) affects every organ system, especially the lungs. Vitamin D has been shown to modulate both infections and autoimmune diseases. It maintains the balance between angiotensin-1 and angiotensin II, thereby preventing lung tissue damage. Hence arises the question - can adequate circulating vitamin D prevent or modulate SARS-CoV-2 infection? In the present study, we attempted to find the answer to this question in the Indian population.

Methodology

-The study duration was April 1, 2020 to April 30, 2021, including only those patients whose vitamin D levels were estimated. Mann-Whitney test was used to compare age, hospital stay, and total vitamin D levels between the two waves. The gender difference, vitamin D status, pre-existing comorbidities, COVID-19 severity, and mortality were calculated using the chi-square test.

Results

- On curating the data, vitamin D levels were found to be estimated in 179 COVID-19 positive patients. In the first wave, 48.2% of the patients were deficient in vitamin D levels, yet no statistical association was observed for patients' demographics (age, sex, and comorbidities), COVID-19 severity, and mortality. Similar results were observed in the second wave. The correlation coefficient of IL-6 (r=-0.08), CRP (r = 0.033), and ferritin (r = 0.027) was not significantly associated with vitamin D levels.

Conclusion

- The Indian population is known to be deficient in vitamin D, yet this study showed an absence of vitamin D correlation with severity, morbidity or mortality of COVID-19. Further research into the immune-modulatory effect of vitamin D on disease susceptibility and progression in COVID-19 would be beneficial.

Introduction

Coronavirus disease 2019 (COVID-19) was declared by World Health Organization (WHO) as a pandemic on March 11, 2020. As of July 4, 2022, approximately 546 million Coronavirus disease-2019 (COVID-19) cases have been registered taking 6.3 million lives [1]. The cumulative percentage of the population affected in India is 3.06% (43 million cases in 1405 million population [2]. Several micronutrients have been associated with the severity of infection with Severe acute respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). One such micronutrient is vitamin D (vit D), a pro-hormone, with a primary role in calcium

and phosphorus absorption and bone mineralization. In addition, it acts as an immune modulator, stimulating innate immunity [3] and down-regulating adaptive immunity [4]. Hence, its deficiency may increase susceptibility to several infections.

During this pandemic, several studies have assessed the role of vit D both in protection against COVID-19 as well as in modulation of the severity of the disease. In some studies, lower vit D was associated with susceptibility to the disease, its severity, and the requirement for mechanical ventilation [5, 6]. On the contrary, other studies found no association between vit D deficiency and COVID-19 severity and mortality [7, 8]. The deficiency of this vital vitamin has been observed in both sunshine deficit and sunshine abundant countries [9]. Although India is a tropical country yet 70–90% of the Indian population is deficient in vit D [10, 11]. Regardless of age, physiological status, or geographic location, the Indian population suffers from hypovitaminosis D [11].

Thus, keeping in view the equivocal outcome and importance of this essential vitamin, the primary end-point of the present study was to assess the evidence of the association between vit D status and the severity and mortality of SARS-CoV-2 infection among the hospitalized patients. The secondary endpoint was to assess the correlation of vit D levels with the levels of inflammatory markers. A comparative analysis between both waves 1 and 2 might provide the crucial answer to whether lower levels of vitamins enhanced the progression of the disease more rapidly among the Indian population who are known to be hypovitaminosis D.

Methodology

In this cross-sectional, comparative retrospective study carried out in a tertiary care center in New Delhi, India, data was extracted from 1st April 2020 to 30th April 2021 to include subjects with COVID-19 in the first (1st April 2020 to 31st December 2020) as well as second waves (1st January 2021 to 30th April 2021) of the pandemic. The study was approved by Institution's Ethics Committee (EC/01/22/1993). All methods were per the relevant guidelines and regulations. Diagnosis and categorization of COVID-19 severity were based on guidelines issued by WHO and Indian Council of Medical Research (ICMR) [12, 13].

Study population and characterization

The data was sifted to include those patients who were RT-PCR positive and who required admission to the hospital and whose vit D levels were available. Patients with negative and inconclusive RT-PCR and those without vit D estimations were excluded from the analysis. Patients were characterized based on their clinical presentation. Those with uncomplicated upper respiratory tract infection and $SpO_2 \geq 94\%$ i.e. without evident breathlessness or hypoxia were defined as mild, those who had pneumonia with no sign of severe disease and SpO_2 90–94%, respiratory rate ≥ 24 per minute with clinical presentation of hypoxia and dyspnea were defined as moderate and those who presented with severe pneumonia and $SpO_2 \leq 90\%$, respiratory rate > 30 per minute with clinical presentation of Acute Respiratory Distress

Syndrome (ARDS) and sepsis were defined as severe [13]. Based on serum vit D concentrations, subjects were classified as deficient (< 20ng/ml), insufficient (20-30ng/ml) and sufficient/normal (> 30ng/ml) [14]. This sifting resulted in the inclusion of 114 patients from the first wave and 65 patients from the second wave of the pandemic (Fig. 1).

Laboratory assays

Serum vit D levels had been measured by Chemiluminescence Immunoassay (CLIA). Interleukin-6 (IL-6) levels had been measured using paramagnetic particle chemiluminescence immunoassay (biological reference interval, BRI- <6.4pg/ml). Ferritin had been determined by chemiluminescent microparticle immunoassay (CMIA) (BRI- 21.8-274.6ng/ml in males and 4.6-204ng/ml in females). C-reactive protein (CRP) had been detected by Nephelometry (Thermo Fischer) (BRI < 1mg/L as non-detectable, 1-10mg/L as mild infection, and > 10mg/L as severe infection) as standardized in the lab of the hospital. These laboratory parameters were estimated during the hospital stay of the patient.

Correlative parameters

- Demographics
- Circulating vit D levels
- COVID-19 severity
- Underlying comorbidities (Patients had more than one comorbid condition)
- Duration of hospital stay
- In-hospital Mortality

Statistical analysis

Association of vit D levels with severity and mortality of COVID-19 were derived for the first and second waves and then compared. For statistical analysis, SPSS version 17.0 software was used (SPSS Inc., Chicago, IL, USA). The data were presented as median (IQR), frequency, and percentages (%). Shaipro Wilk test was conducted to check the distribution of the data. The chi-square test was used to compare the differences in categorical variables among the groups. The Mann-Whitney test was used to test the significance of variables (continuous) between two groups that did not demonstrate normality. The Kruskal Wallis test was used for the comparison of age, and hospital stay between levels of vit D. Correlation coefficient (r) was determined by Spearman Test. Cytokine levels in vit D deficient (< 20ng/ml), insufficient (20-30ng/ml), and sufficient (> 30ng/ml) subjects were depicted using Box and Whiskers graphs. p-value ≤ 0.05 was considered significant.

Results

Clinical characteristics of COVID-19 patients based on their vitamin D status

Of the 179 RT-PCR confirmed cases of COVID-19 who needed hospital admission, 88 (49.1%) were deficient in vit D, 45 (25.1%) were insufficient and 46 (25.6%) were sufficient. The median age of subjects with deficient vit D levels was 54.5 (40–65) years, with insufficient levels was 57 (32.5–67.5) years and with sufficient levels was 62.5 (46.75–72.5) years. The male gender was found to be more prevalent in all the three groups (65.9% in deficient, 68.9% in insufficient, and 67.4% in sufficient). Most of the patients had moderate disease with hypertension being the most common co-morbid condition. Hospital stay and mortality were also similar in all the three groups as detailed in Table 1a and 1b. Categorizing the patients on basis of their circulating vit D levels did not show a significant correlation with severity, comorbidities, hospital stay, and mortality (Tables 1a,b).

Table 1
a: Clinical characteristics based on vitamin D levels

Variables	**Vit D deficient (n = 88)**	**Vit D insufficient (n = 45)**	**Vit D sufficient (n = 46)**
¶**Age in years** Median (IQR)	54.5 (40–65)	57 (32.5–67.5)	62.5 (46.75–72.5)
#Gender- Male	58 (65.9%)	31 (68.9%)	31 (67.4%)
Female	30 (34.1%)	14 (31.1%)	15 (32.6%)
# **COVID-19 Severity-**	1 (1.1%)	2 (4.4%)	3 (6.5%)
Mild	53 (60.2%)	24 (53.3%)	29 (63.04%)
Moderate	34 (38.6%)	19 (42.2%)	14 (30.4%)
Severe			
# **Comorbidities**	34 (38.6%)	15 (33.3%)	19 (41.3%)
Diabetes	42 (47.7%)	19 (42.2%)	24 (52.1%)
Hypertension	30 (34.09%)	19 (42.2%)	19 (41.3%)
CKD	19 (21.5%)	7 (15.5%)	7 (15.2%)
HD			
¶**Hospital stay [Median (IQR)]**	11.5 (7-24.25)	12 (6-26.25)	11 (4–20)
# **Mortality**	26 (29.5%)	13 (28.8%)	11 (23.9%)
¶Kruskal wallis test; # Chi-squared test			

Table 1
b: Significance of clinical characteristics based on vitamin D levels

Variables	Deficient vs Insufficient (p value)	Deficient vs Sufficient (p value)	Insufficient vs Sufficient (p value)
¶**Age**- Median (IQR)	0.964	0.117	0.231
#Gender- Male Female	0.730	0.863	0.878
COVID-19 Severity- Mild Moderate Severe	0.410	0.170	0.492
Comorbidities- Diabetes Hypertension CKD HD	0.549 0.547 0.358 0.406	0.764 0.625 0.410 0.376	0.432 0.342 0.929 0.964
Hospital stay	0.776	0.380	0.750
Mortality	0.937	0.489	0.590

Clinical characteristics of COVID-19 patients: a comparison between first and second wave

The data in the first wave was sifted and compared with the data in the second wave. Data from the first wave included 114 COVID-19 positive patients and that from the second wave included 65 subjects. The percentage of subjects with deficient vit D levels was similar in both waves (48.2% and 50.8% in the first and second waves, respectively). The percentage of those with insufficient and sufficient circulating vit D levels was also similar in the two waves (23.7% and 28.1% in the first wave; 27.7% and 21.5% in the second wave, respectively) as detailed in Table 2.

The median age of patients was 57.5 years and 55 years in the first and the second waves, respectively, with a predominance of male gender in both the waves (77/114 versus 43/65).

The Median (IQR) level for vit D was 20.4ng/ml (9.8-30.7ng/ml) in the first wave and 19.7ng/ml (12.9-28.5ng/ml) in the second wave.

The majority of the patients were admitted with moderate (59.22%) to severe forms (37.43%) of the disease in both waves. In the first wave, the percentage of patients with moderate disease (66.7%) was twice as many as those with severe disease (30.7%). On the other hand, in the second wave, the percentage of subjects with moderate and severe disease was similar (46.2% and 49.2%, respectively).

The most common comorbidity in both waves was hypertension [HTN] (n = 53/114; n = 32/65 respectively) followed by Type-2 diabetes mellitus [DM]; (n = 39/114; n = 29/65 respectively), chronic kidney disease [CKD] (n = 44/114; n = 24/65 respectively) and coronary artery disease [CAD]; (n = 21/114; n = 12/65 respectively)]. Other comorbidities observed were tubercular meningitis, iron deficiency, sarcoidosis, hypothyroidism, obesity, rheumatoid arthritis, and chronic liver disease.

In both the waves, the duration of hospital stay [12 (6–28) days versus 10 (6–17)] and mortality rate (29% versus 24%) were similar (Table 2).

Table 2
General demographics and clinical presentations of patients (first vs second wave)

Parameters- Variables	Wave 1 (n = 114)	Wave 2 (n = 65)	p-value
¶**Age**- Median (IQR)	57.5 (37–67)	55 (46.5–68.5)	0.443
#Gender- Male	77 (67.5%)	43 (66.2%)	0.849
Female	37 (32.5%)	22 (33.8%)	
¶**Vitamin D levels**- Median (IQR)	20.4 (9.8–30.7)	19.7 (12.9–28.5)	0.927
#Vitamin D status-	55 (48.2%)	33 (50.8%)	0.605
Deficient (< 20ng/ml)	27 (23.7%)	18 (27.7%)	
Insufficient (20-30ng/ml)	32 (28.1%)	14 (21.5%)	
Sufficient (> 30ng/ml)			
#COVID-19 severity	3 (2.6%)	3 (4.6%)	0.036*
Mild	76 (66.7%)	30 (46.2%)	
Moderate	35 (30.7%)	32 (49.2%)	
Severe			
#Comorbidities-	39 (34.2%)	29 (44.6%)	0.168
Diabetes	53 (46.5%)	32 (49.2%)	0.724
Hypertension	44 (38.6%)	24 (36.9%)	0.824
Chronic kidney disease	21 (18.4%)	12 (18.5%)	0.995
Coronary artery disease			
¶**Hospital stay** in days Median (IQR)	12 (6–28)	10 (6–17)	0.107
#Mortality	34 (29.8%)	16 (24.6%)	0.455
¶Mann Whitney U test; # Chi-squared test			
*p value < 0.05, statistically significant			

Clinical characteristics of COVID-19 patients based on vitamin D status: a comparison between first and second wave

Further, comparing data from the two waves, the percentage of subjects with comorbid hypertension was significantly higher in wave 2 in those with insufficient vit D levels. No significant difference in other prevailing comorbidities was observed in relation to vit D status (Table 3). The median (IQR) length of

hospital stay amongst patients in wave 1 and wave 2 was also similar in vit-D deficient [14.5 (8–28) and 10 (5.5–15) days, respectively], insufficient [10 (5.2–26.2) and 13 (7-26.5) days, respectively] and sufficient [16 (5–20) and 7.5 (3-16.7) days, respectively] patients.

Table 3
Patient's characteristics based on levels of vitamin D

	VITAMIN- D LEVELS					
PARAMETERS-VARIABLES	**DEFICIENT**		**INSUFFICIENT**		**SUFFICIENT**	
N (%)	**Wave 1 (n = 55)**	**Wave 2 (n = 33)**	**Wave 1 (n = 27)**	**Wave 2 (n = 18)**	**Wave 1 (n = 32)**	**Wave 2 (n = 14)**
¶**Age**- Median (IQR)	58 (39–66)	53 (45–61)	57 (25–64)	61.5(49.5–72.5)	57 (39.75–71.5)	64.5 (53.25–74.5)
p-value	0.372		0.057		0.424	
Gender- Male	39 (70.9%)	19 (57.6%)	16 (59.3%)	15 (83.3%)	22 (68.8%)	9 (64.3%)
Female	16 (29.1%)	14 (42.4%)	11 (40.7%)	3 (16.7%)	10 (31.3%)	5 (35.7%)
p-value	0.201		0.111		0.766	
COVID-19 severity Mild	1 (1.8%)	0 (0%)	0 (0%)	2 (11.1%)	2 (6.3%)	1 (7.1%)
Moderate	36 (65.5%)	17 (51.5%)	18 (66.7%)	6 (33.3%)	22 (68.8%)	7 (50%)
Severe	18 (32.7%)	16 (48.5%)	9 (33.3%)	10 (55.6%)	8 (25%)	6 (42.9%)
p-value	0.274		0.089		0.455	
Comorbidities- Diabetes	19 (34.5%)	15 (45.5%)	8 (29.6%)	7 (39.8%)	12 (37.5%)	7 (50%)
p-value	0.309		0.519		0.428	
Hypertension	27 (49.1%)	15 (45.5%)	8 (29.6%)	11 (61.1%)	18 (56.3%)	6 (42.9%)
p-value	0.741		0.036		0.403	
Chronic kidney disease	19 (34.5%)	11 (33.3%)	10 (37%)	9 (50%)	15 (46.9%)	4 (28.6%)
p-value	0.908		0.388		0.335	
Heart disease	12 (21.8%)	7 (21.2%)	4 (14.8%)	3 (16.7%)	5 (15.6%)	2 (14.3%)
p-value	0.947		1.00		1.00	

*Mann Whitney U test; Chi-squared test (all others)

	VITAMIN- D LEVELS					
¶**Hospital stay** Median (IQR)	14.5 (8–28)	10 (5.5–15)	10 (5.25–26.25)	13 (7-26.5)	16 (5–20)	7.5 (3-16.75)
p-value	0.052		0.408		0.206	
Mortality	17 (30.9%)	9 (27.3%)	8 (29.6%)	5 (27.8%)	9 (28.1%)	2 (14.3%)
p-value	0.717		0.893		0.460	
*Mann Whitney U test; Chi-squared test (all others)						

Inflammatory markers and vitamin D status in COVID-19 patients

We also determined the association between levels of circulating vitamin D and inflammatory markers associated with cytokine storm (IL-6, ferritin and CRP), in order to estimate the plausible role of vit D in COVID 19 morbidity. No statistically significant correlation was observed between circulating vit D and levels of IL-6 (r= -0.088, p = 0.949), Ferritin (r = 0.027, p = 0.345) and CRP (r = 0.033, p = 0.116) as shown in Fig. 2 (a)-(c). Interestingly, when comparing these inflammatory markers with vit D status (median and IQR), CRP was found to be significantly lower in the subjects with insufficient vit D compared to those with deficient vit D (p = 0.048); Fig. 2 (c).

Survival analysis

Finally, a survival analysis of patients with deficient, insufficient, and sufficient levels of vit D was carried out in both the waves (Fig-3). In wave 1, patients with deficient vit D had a higher mortality risk than patients with insufficient and sufficient levels (fig 3a). Another feature observed was that patients with insufficient and sufficient vit D levels survived more than 150 days post-infection and then succumbed to death. The scenario in wave 2 was very different. Herein, the early mortality rate was less among patients with vit D deficient and insufficient levels than patients who had sufficient vit D levels (fig 3b).

Discussion

The ongoing COVID-19 pandemic has affected millions across the globe not only physically but also psychologically and economically. It has highlighted many gaps in our knowledge of human physiology, including genetic-biochemical reactions of infection and immune regulatory response to challenges with unknown etiology. Studies have been conducted to understand the patients' characteristics in the first and second waves of the pandemic. With the emergence of newer mutant strains, the second wave was more intense in terms of oxygen and ventilation requirement, disease spread, and positivity rate as reported by Jain VK *et al.* [15]. They also reported increased breathlessness and infectivity rate among younger patients in the second wave. Overall, COVID-19 has resulted in a huge loss of human life. Thus, it

is of paramount importance to investigate the risk factors for the transmission of SARS-CoV-2 infection as well as the clinical course of COVID-19.

During the pandemic, several studies have attempted to decipher the plausible role of micronutrients in protecting against COVID-19 severity and mortality. One such micronutrient is vit D. Earlier studies have shown a correlation between incidences of respiratory tract viral infection and 25-hydroxyvitamin D levels [16].

In this scenario, deciphering the plausible role of micronutrients in protecting against COVID-19 severity and mortality, especially vitamin D deficiency may represent an easily modifiable risk factor, particularly considering the limited cost and the safety of vitamin D supplementation. Interestingly, 50% of the present study cohort was deficient in vit D, yet the findings from our study observed no significant correlation between vit D status (deficient, insufficient, and sufficient) and COVID-19 severity and mortality. Our data corroborated with findings from other studies. Jevalikar *et al.* in a tertiary care center in New Delhi, India carried out a prospective, observational study and observed that 48.2% (n = 197/410) of their study population was deficient in vit D. The authors found no association between levels of vit D and COVID-19 severity and mortality. They also concluded that vit D deficiency was not associated with levels of inflammatory markers [7]. Another study comprising people from 24 Asian countries observed that the number of patients with COVID-19 infections and mortalities did not show a significant correlation when the mean Vit D levels were used alone but when the other confounding factors were taken into account, the number of COVID-19 infections and mortalities were significantly correlated [17]. A study carried out an analysis on 348,598 subjects obtained from UK Biobank data. Among these, 449 subjects were diagnosed with COVID-19 infection. They did not find any association between levels of vit D and COVID-19 infection either on univariate or multivariate analyses [18]. Hernandez *et al.* in a cohort of 216 COVID-19 patients also found no association between vit D deficiency and COVID-19 severity including ICU admission, mechanical ventilation, and mortality [8]. A meta-analysis and systematic review of 26 studies including 8176 COVID-19 patients observed no association of the risk of COVID-19 infection with vit D deficiency. However, vit D deficient subjects had significantly severe disease [19].

On the contrary, a few studies differ in their outcomes with respect to the role of vit D in COVID-19. Very recently, Dror *et al.* observed that patients with insufficient vit D levels prior to infection, had severe COVID-19 and increased mortality rate during hospitalization [20]. Israel and colleagues analyzed the level of vit D in 5,76,455/13,59,399 subjects between 2010 to 2019. Of these, 52,405 were subsequently COVID-19 positive and 5,24,050 served as controls. A significant association of lower levels of vit D with the risk of SARS-CoV-2 infection was noted [21]. Hyoung *et al.* in their study found that 67% of mild COVID-19 patients were deficient in vit D at the time of presentation. They further elucidated that 80% of the vit D deficient subjects had severe disease and required mechanical ventilation [5]. Two other independent studies carried out by Kaufman *et al.* and Meltzer *et al.* found lower levels of vit D correlated with SARS-CoV-2 positivity [22, 23]. Other small cohort studies detected a positive association between vit D deficiency/insufficiency and COVID-19 severity [6, 24–28].

Thus, literature regarding the association between vit D levels and COVID-19 severity is equivocal. The variability in findings may be attributed to the different cohorts of patients wherein some studies included asymptomatic or mild cases while others included only moderate to severe cases. Moreover, some studies had a very low sample size.

Further using Mann Whitney test/Chi-squared test, we performed a comparison between the levels of vit D, diseases' status (severity), survival/mortality rate, and the effect of pre-existing comorbidities among COVID-19 patients of waves 1 and 2. Our analysis did not show any significant correlation between levels of vit D, disease severity, and comorbid conditions except for existing hypertension ($p = 0.036$) among those who had insufficient vit D levels. An interesting observation in our study was the survival status among COVID-19 patients with deficient/insufficient vit D. Although a distinct outcome was observed between waves 1 and 2, it appears to be independent of levels of vit D.

To the best of our knowledge, this is the first study to highlight that lower levels of vit D are not responsible for poor prognosis in COVID-19 infected Indian patients comparing both the first and second waves of the pandemic in India. In fact, a recent study carried out by two of the investigators of this team showed that 79.05% of Indians suffer from vitamin D deficiency (hypovitaminosis), and an additional 10.88% have insufficient vitamin D levels (unpublished; EC/05/19/1525). Knowing this fact, our study analysis provided a very useful outcome, especially for Indian patients suffering from SARS-CoV-2 infection.

To further substantiate our findings, we performed the coefficient correlation analysis of levels of IL6, ferritin, and CRP among the COVID-19 patients and their vit D levels. The study revealed that levels of the above markers of cytokine storm, the hallmark of COVID-19 severity were not significantly higher among vit D deficient COVID-19 patients. This outcome reflects the data of our analysis that showed that the severity of the disease does not correlate to vit D levels. Pizzini *et al.*, in their study of 109 patients, observed that vit D deficiency did not correlate with levels of pro-inflammatory cytokines (IL-6, CRP, ferritin, and D-dimer) [29]. Another recent study by Jevalikar *et al.* also showed no statistical significance between vit D deficiency and disease severity and inflammatory markers (IL-6, CRP, and ferritin) in a cohort of 410 COVID-19 patients [7].

Although this study was carried out before the third wave (Omicron variant), the resulting outcome most likely will not be affected since the SARS-CoV-2 virus has not changed substantially to negate the effect of vit D. In this study, vit D was not re-evaluated before discharge and hence those on supplementation were not mentioned. There is need to find out the mechanistic pathway responsible that could have a direct or indirect role in COVID-19.

Conclusion

In summary, our retrospective study suggests an absence of association between vit D levels in COVID-19 severity (clinical and biochemical) and mortality in a North Indian urban population. Further evaluation of

the immune-modulatory effect of vit D in susceptibility and course of disease in COVID-19 would be pertinent as the Indian population is known to have hypovitaminosis D.

Declarations

Author contributions:

All authors contributed and approved the final manuscript. YC collated the data, reviewed the literature, and drafted the manuscript; SB conceptualized, guided, edited, and proofread; SAB aided in the collation of data and proofreading; SPB advised and suggested the result outcomes, proofread the manuscript; AK and AG extracted demographic and clinical details; PC performed statistical analyses; SC conceptualized, guided, analyzed the data, framed the questions, edited the manuscript and proofread.

Conflict of interest

The authors declare that they do not have any conflict of interest.

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Figures

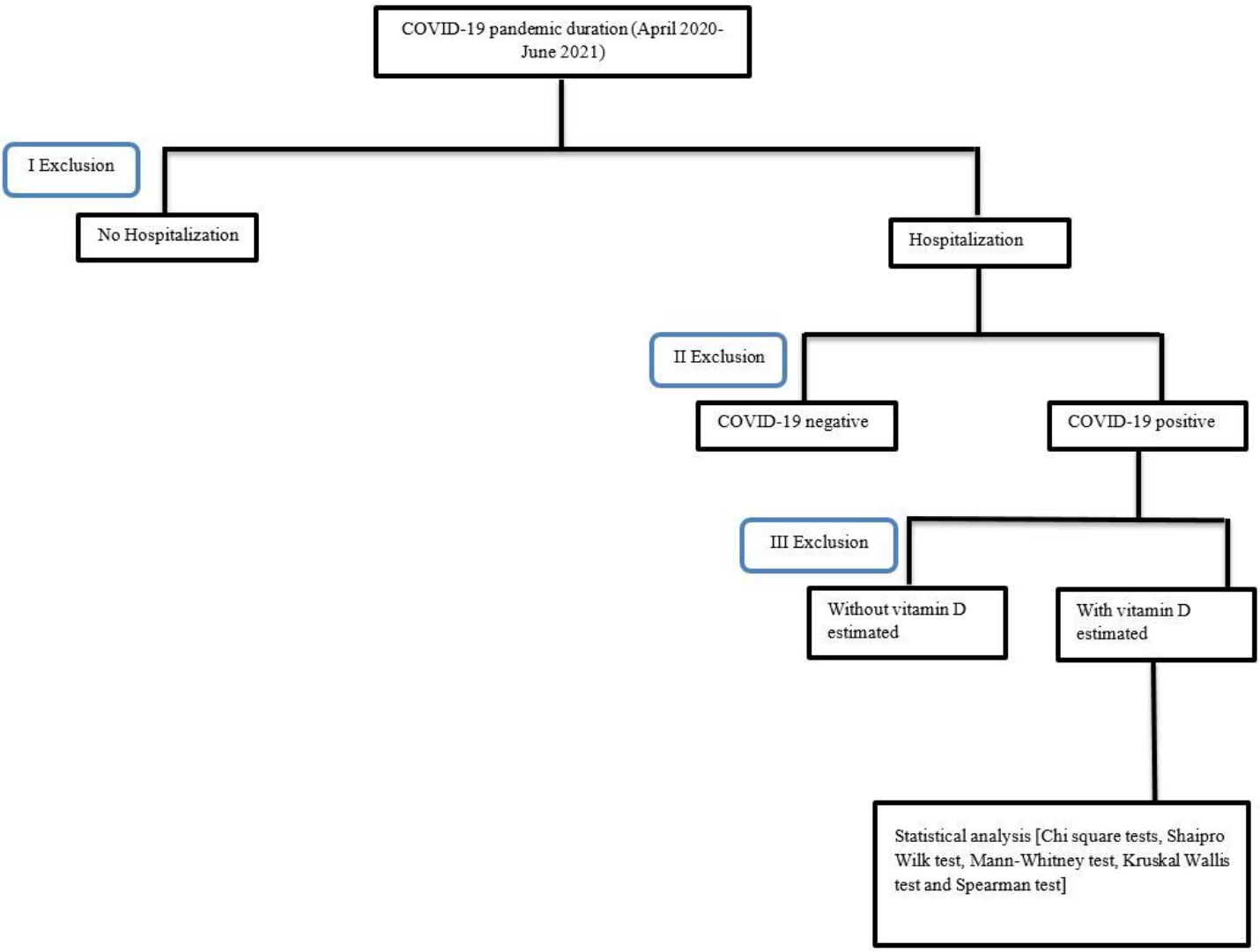

Figure 1

Flowchart of study enrolment

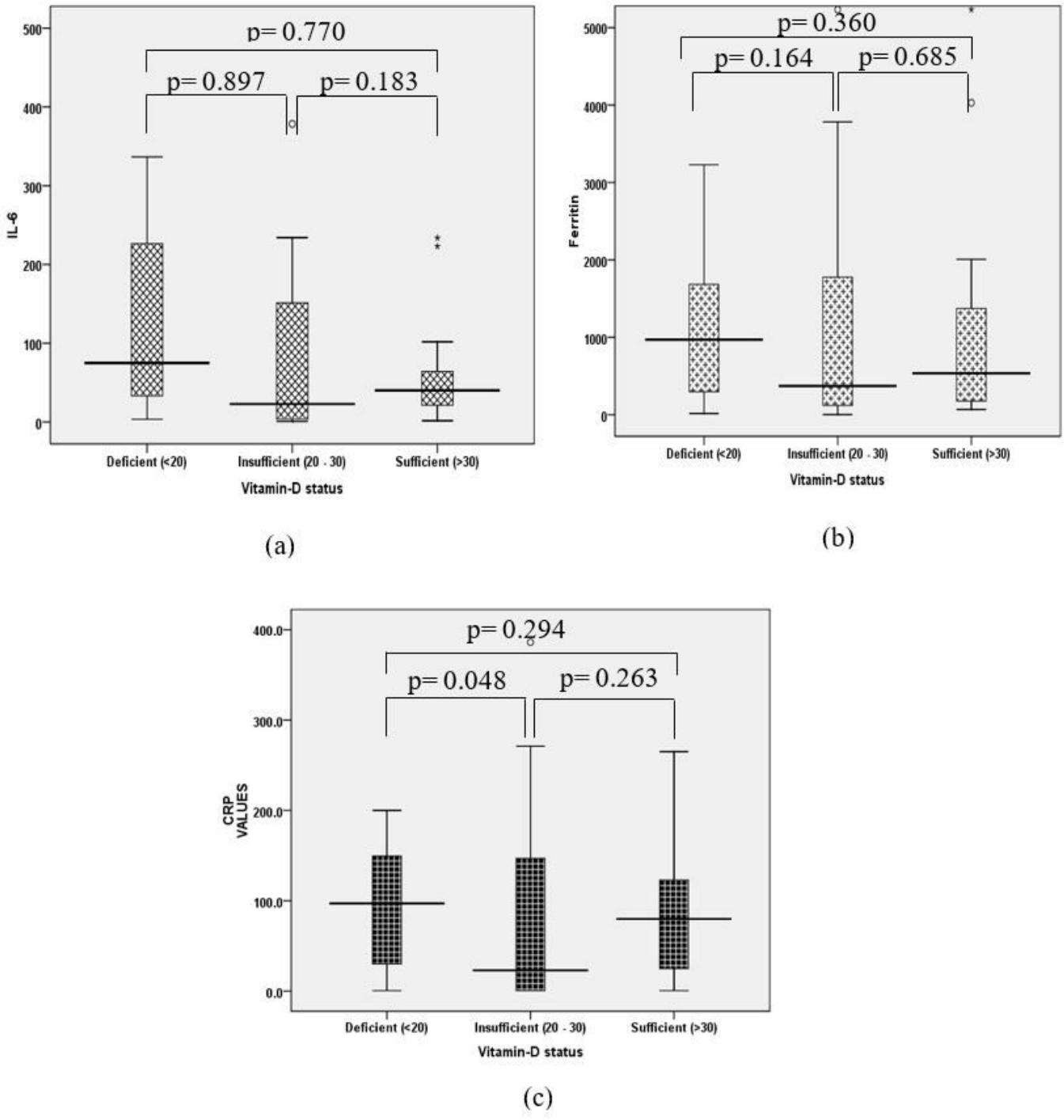

Figure 2

Box and whiskers graph showing cytokine levels in three groups of vitamin D deficient (<20ng/ml), insufficient (20-30ng/ml) and sufficient (>30ng/ml); (a) IL-6 (b) Ferritin (c) CRP

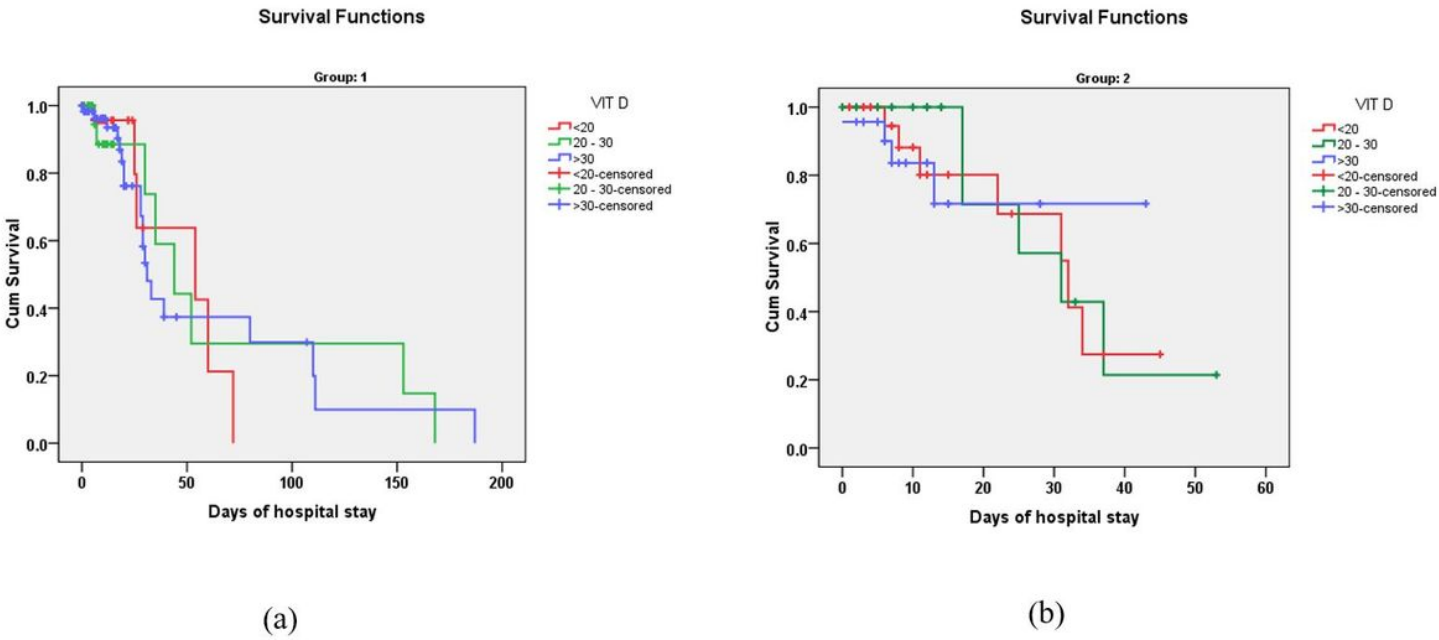

Figure 3

Kaplan Meier curve showing survival in three groups of subjects - vitamin D deficient (<20ng/ml), insufficient (20-30ng/ml) and sufficient (>30ng/ml); (a) wave 1 (b) wave 2