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**Original Research Paper** 

Endocrinology

## STUDY OF VITAMIN D LEVELS AND CLINICAL OUTCOMES IN PATIENTS WITH COVID-19 INFECTION

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ABSTRACT Background: COVID-19 is an infectious disease associated with the increased production of proinflammatory cytokines, increased risk of pneumonia, sepsis and acute respiratory distress syndrome. There is accumulating evidence on Vitamin D and its antiviral, immunomodulatory and anti-inflammatory actions. Present study was aimed to correlate serum vitamin D levels and clinical outcomes of patients with COVID 19. Material and Methods: The present study was hospital based observational study, conducted in patients 18 years of age and older with acute respiratory tract infection symptoms with definitive diagnosis of COVID-19 with real-time polymerase chain reaction (RT-PCR). Results: In present study 100 patients were studied. There was no statistically significant difference found between Survivors and Non Survivors with respect to age, gender. 18 % mortality was noted in present study. High risk factors such as diabetes mellites, hypertension, acute kidney injury, COPD & hepatitis were significantly noted in non-survivors as compared to survivors & difference was statistically significant. There was a statistically significant difference found between survivor and non-survivor with respect to LDH levels, ferritin levels & Vitamin D levels. There was a statistically significant difference found between outcome and Vitamin D levels (p value 0.004) while, there was no statistically significant difference found between Comorbidities and Vitamin D levels (p value 0.117). Conclusion: In present study serum vitamin D deficiency was directly associated with the increased risk of mortality in COVID-19 infection. There is need for research, whether vitamin D has specific effects against novel coronavirus in patients with COVID-19 infection.

## KEYWORDS : vitamin D deficiency, risk of mortality, COVID-19 infection, coronavirus

#### INTRODUCTION

COVID-19 is an infectious disease associated with the increased production of pro-inflammatory cytokines, increased risk of pneumonia, sepsis and acute respiratory distress syndrome. Several risk factors, such as older age, ethnicity, raised body mass index (BMI), the presence of diabetes mellitus, and cardiovascular disease, are postulated to be associated with increased risk of infection and subsequent progression to critical illness.<sup>1</sup>

Vitamin D (Vit D) is a fat-soluble vitamin that plays major role in calcium homeostasis. It is synthesized endogenously in the skin when exposed to Ultraviolet-B (UV-B) radiations in sunlight. 1,25-dihydroxy vitamin D [1,25-(OH)2 D] is the active form of Vit D.<sup>2</sup> Vitamin D deficiency is pandemic, yet it is the most underdiagnosed and undertreated nutritional deficiency in the world. Even in tropical countries such as India, vitamin D deficiency prevails in 40%–99% of population, with most of the studies reporting a prevalence of 60%–90%.<sup>3</sup>

There is Accumulating evidence on Vitamin D and its antiviral, immunomodulatory and anti-inflammatory actions.<sup>4</sup> Considering the impact of the COVID-19 risk that potentially results from low vitamin D status, several studies have explored this association. However, the results of these studies are conflicting. Present study was aimed to correlate serum vitamin D levels and clinical outcomes of patients with COVID 19.

### MATERIAL AND METHODS

The present study was hospital based observational study, conducted in the department of General Medicine at R L Jalappa hospital, Kolar during (MENTION STUDY PERIOD) .

of COVID-19 with real-time polymerase chain reaction (RT-PCR).

- Exclusion criteria: Pregnant women, patients not willing to participate.
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Informed written consent was taken from all patients participating in the study. Patients underwent history recording, general physical examination. Laboratory investigations such as complete blood count, plasma glucose, blood urea, serum creatinine, serum electrolytes, liver function tests, vitamin D levels, serum ferritin, LDH, D-dimers and CRP levels were done in all patients. X ray chest was done in all patients & ECG, HRCT was done whenever indicated. Patients were managed as per standard Guidelines and Protocol given by government of India.

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Non-parametric Chi-square and t test was used for comparative analysis results between different groups and to find significance (p) value. Continuous data was represented as mean and standard deviation. P value of <0.05 was considered as statistically significant.

#### RESULTS

In present study 100 patients were studied. There was no statistically significant difference found between Survivors and Non Survivors with respect to age, gender. 18 % mortalityatients with fever, cough and breathlessness visiting the Emergency Department at RL Jalappa hospital, Kolar were considered for the study. Ethical committee approval was obtained.

 Inclusion criteria: Patients 18 years of age and older with acute respiratory tract infection symptoms with definitive

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diagnosis was noted in present study. High risk factors such as diabetes mellites, hypertension, acute kidney injury, COPD & hepatitis were significantly noted in nonsurvivors as compared to survivors & difference was statistically significant.

| Parameter           | Survivors (n=<br>82) | Non Survivors $(n = 18)$ | P value |
|---------------------|----------------------|--------------------------|---------|
| Mean age (in years) | 51.21 ± 14.2         | 57.54 ± 15.43            | 0.68    |
| Gender              |                      |                          |         |
| Male                | 47 (57.32 %)         | 11 (61.11 %)             | 0.53    |
| Female              | 35 (42.68 %)         | 7 (38.89 %)              |         |
| High risk factors   |                      |                          |         |
| Diabetes Mellites   | 28 (34.15 %)         | 13 (72.22 %)             | < 0.01  |
| Hypertension        | 29 (35.37 %)         | 9 (50 %)                 | < 0.01  |
| Acute kidney injury | 7 (8.54 %)           | 9 (50 %)                 | < 0.01  |
| COPD                | 5 (6.1 %)            | 6 (33.33 %)              | < 0.01  |
| Hepatitis           | 1 (1.22 %)           | 4 (22.22 %)              | < 0.01  |
| Ischemic Heart      | 4 (4.88 %)           | 2 (11.11 %)              | 0.32    |
| Disease             |                      |                          |         |
| Chronic Kidney      | 1 (1.22 %)           | 2 (11.11 %)              | 0.20    |
| Disease             |                      |                          |         |
| Thyroid disorders   | 4 (4.88 %)           | 1 (5.56 %)               | 0.54    |

#### Table 1:-General characteristics

Mean LDH levels among non-survivor was 976.11  $\pm$  482.48 and Mean LDH levels among Survivor was 337.4  $\pm$  176.38. There was a statistically significant difference found between survivor and non-survivor with respect to LDH levels. Mean ferritin levels among non-survivor was 761.38  $\pm$  316.15 and Mean ferritin levels among Survivor was 306.52  $\pm$  288.64. There was a statistically significant difference found between survivor and non-survivor with respect to ferritin levels.

Mean Vitamin D levels among non-survivor was  $17.65 \pm 6.8$ and Mean Vitamin D levels among Survivor was  $25.03 \pm 11.55$ . There was a statistically significant difference found between survivor and non-survivor with respect to Vitamin D levels.

# Table 2:- Comparison of LDH, Ferritin and Vitamin D levels according to outcome.

| Parameter | Survivor (Mean<br>± SD) | Non-survivor<br>(Mean ± SD) | P value |
|-----------|-------------------------|-----------------------------|---------|
| LDH       | 337.40 ± 176.38         | 976.11 ± 482.48             | < 0.001 |
| FERRITIN  | $306.52 \pm 288.64$     | 761.38 ± 316.15             | < 0.001 |
| Vitamin D | $25.03 \pm 11.55$       | $17.65 \pm 6.80$            | 0.001   |

There was a statistically significant difference found between outcome and Vitamin D levels (p value 0.004) while, there was no statistically significant difference found between Comorbidities and Vitamin D levels (p value 0.117). Mean duration of hospital stay among subjects with Vitamin D deficiency was  $16.39 \pm 13.76$  days and Mean duration of hospital stay among subjects with normal Vitamin D was  $10.48 \pm 4.2$  days. There was a statistically significant difference found between subjects with Vitamin D deficiency and subjects with normal Vitamin D with respect to duration of hospital stay (p value 0.002).

Table 3:- Distribution of subjects according to comorbidities and Vitamin D levels

| Parameter        | Vitamin D<br>deficiency | Normal<br>Vitamin D     | P value |
|------------------|-------------------------|-------------------------|---------|
|                  | (< 20 ng/mL)            | ( <u>&gt;</u> 20 ng/mL) |         |
| No comorbidities | 7 ( 22.6%)              | 27 (39.1%)              | 0.117   |
| Comorbidities    | 24 ( 77.4%)             | 42 (60.9%)              |         |
| Survivor         | 20 (64.5%)              | 62 (89.9%)              | 0.004   |
| Non-survivor     | 11 (35.5%)              | 7 (10.1%)               |         |

| Μ  | ean duration of     | $16.39 \pm 13.769$ | 10.48 ± | 0.002 |
|----|---------------------|--------------------|---------|-------|
| ho | ospital stay (days) |                    | 4.276   |       |

#### DISCUSSION

Coronavirus disease (COVID-19) is a respiratory and systemic disorder caused by "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" with a range of severity from mild respiratory symptoms to severe lung injury, multi-organ failure, and death.

Vitamin D (also referred to as "calciferol") is a fat-soluble vitamin that is naturally present in a few foods, added to others, and available as a dietary supplement. It is also produced endogenously when ultraviolet (UV) rays from sunlight strike the skin and trigger vitamin D synthesis. As strongly suggested by genetic, molecular, cellular, and animal studies, extraskeletal effects related to vitamin D signaling include roles in cell proliferation, immune and muscle function, skin differentiation, and reproduction, with vitamin D having vascular and metabolic actions as well.<sup>5</sup>

Vitamin D [1,25-dihydroxyvitamin D; 1,25(OH)2D], interacting with its receptor (VDR) in immune cells, modulates the innate and acquired immune systems in response to invasion of bacterial and viral pathogens. <sup>6</sup> Therefore, vitamin D might help in treatment of COVID-19 by preventing the cytokine storm and subsequent ARDS which is commonly the cause of mortality.

Our body's innate and adaptive immune system provides protection against viral infections and aids in regulating cytokine levels in young and elderly populations, respectively. Vit D has been widely implicated in enhancing the immune response and suppressing the cytokine storm.<sup>7</sup>

Some of the previous studies which have been done on relation of VIT D levels in COVID 19 have shown higher level of inflammatory markers like CRP(surrogate marker of vit D) and higher severity and complication rates among patients. With vit D deficiency.<sup>8</sup> A meta-analysis of randomize control trials shows that improving the vitamin D status in children and adults has been associated with reduced risk of upper or lower respiratory tract infections.<sup>9</sup>

In India, Glicio et al., studied 176 COVID-19 patients 60 years or older, over 80% were vitamin D insufficient or deficient, and of those, 72% were male. Inadequate 25(OH)D was strongly associated with chronic kidney disease, hypertension, and diabetes. Insufficient 25(OH)D was found in 45% of the 24 patients with mild COVID-19 vs. 86% of the 131 patients with severe outcomes.<sup>10</sup> Similar findings were noted in present study.

Alipio et al<sup>11</sup> noted that as the severity of disease increased from mild to critical, serum 25OHD levels decreased from 31.2 ng/ml to 17.1 ng/ml and were statistically significant with clinical outcomes. Out of 212 patients, 80 exhibited Vit D insufficiency (25 OHD<21-29 ng/ml) and 77 exhibited Vit D deficiency (25 OHD<20 ng/ml). The odds of having mild clinical outcome increases and critical outcome decreases, with increase in serum 25 OHD level.

Anshul Jain et al.,  $^{\rm 12}$  noted that vitamin D deficiency (serum 25 (OH)D concentration <20 ng/mL) is far more prevalent in patients with severe COVID–19 disease requiring ICU admission and thereby increased chances of mortality. For non-skeletal purpose many researchers had suggested cutoff level of serum 25 (OH)D to <30 ng/ml for defining vitamin D deficiency15, on adopting this criterion the prevalence was almost 100% in critically ill patients (62 out of 63).

In a systematic review and meta-analysis by Nanyang Liua et

al.,<sup>13</sup> noted that low vitamin D status might be associated with an increased risk of COVID-19 infection. 361,934 participants were selected for meta-analysis. Overall, vitamin D deficiency or insufficiency was associated with an increased risk of COVID-19. In addition, COVID-19-positive individuals had lower vitamin D levels than COVID-19-negative individuals.

To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40–60 ng/mL (100–150 nmol/L).<sup>14</sup>

Major limitations of present study were prevalence of vitamin D deficiency in present locality is not estimated, interval between actual infection and admission was not been taken in consideration and pro-inflammatory markers were not adjusted with other co-morbidities like diabetes and hypertension. Multicenter study with large number of subjects is recommended to confirm findings.

#### CONCLUSION

In present study serum vitamin D deficiency was directly associated with the increased risk of mortality in COVID-19 infection. There is need for research, whether vitamin D has specific effects against novel coronavirus in patients with COVID-19 infection.

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