Indonesian Journal of Medical Laboratory Science and Technology
Open Access
p-ISSN 2684-6748
e-ISSN 2656-9825

RESEARCH ARTICLE

# Analysis of bone mineral profile and TSH in early non-dialysis stages of chronic kidney disease - a retrospective cross-sectional study

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*Article history:*
Received: 2024-05-11
Revised: 2024-07-18
Accepted: 2024-09-11
Available online: 2024-10-31

*Keywords:*
Glomerular filtration rate
Thyrotropin
Chronic kidney disease-mineral and bone disorder
Kidney diseases

https://doi.org/10.33086/ijmlst.v6i2.5864

## Abstract

The objective of this study is to analyse the levels of Thyroid stimulating hormone (TSH) and the Bone Mineral Profile (Vitamin D, Parathyroid hormone (PTH), calcium, phosphorus, magnesium, and alkaline phosphatase [ALP]) levels in the early stages of chronic kidney disease (CKD) based on Glomerular filtration rate (GFR). A retrospective analysis was conducted involving 247 CKD patients admitted to the nephrology department at Sri Ramachandra Medical College Hospital from January to June 2022. The estimated GFR (eGFR) was calculated utilizing the CKD-EPI formula provided by the National Kidney Foundation. All biomarkers were analysed using automated platforms. The baseline ages for the three groups were 52.5, 68, and 66.5 years respectively ($p<0.001$). The comparative analysis revealed statistically significant differences solely among Vitamin D, creatinine, PTH, and phosphorus across the three groups. Further correlation analysis demonstrated changes in bore significant correlations with only creatinine, vitamin D, and PTH. This study concludes that in the early stages of CKD, vitamin D followed by PTH appears to be the earliest biomarker for assessing CKD-Mineral and Bone Disorder (CKD-MBD) occurring prior to any alterations in calcium and phosphate levels. As such, early consideration of supplementation may prove beneficial in mitigating disease progression and preventing cardiovascular complications.

## 1. INTRODUCTION

Chronic Kidney Disease (CKD) represent a significant global health challenge due to its prolonged course, diminished quality of life, and dependency on dialysis. The complications associations with CKD contribute to considerable morbidity and mortality, resulting in escalating healthcare expenditures. A ccording to the 2023 guidelines issued by Kidney Disease: Improving Global Outcomes (KDIGO), CKD is characterized by

**Citation:** Rajan IR, Elango K, Selvarajan S, Krishnamurty S, Sathyamoorthy SK. Analysis of bone mineral profile and TSH in early non-dialysis stages of chronic kidney disease - a retrospective cross-sectional study. Indones J Med Lab Sci Technol. 2024;6(2):151–158. https://doi.org/10.33086/ijmlst.v6i2.5864

abnormalities in kidney structure or function that persist for more than three months, accompanied by related health implications. Typically, CKD is defined by a glomerular filtration rate (GFR) of less than 60 mL/min (G3a – G5). In the early stages (G1& G2), where the GFR exceeds 60mL/min, CKD only when there is evidence of kidney damage (1). As of the 2022 update, the estimated prevalence of CKD is approximately 843.6 million with a higher incidence observed in women, older adult populations, and individuals with diabetes mellitus or hypertension. The mortality rate attributable to CKD and its complications has risen to 41.5% from 1990 to 2017 (2).

CKD disrupts vitamin D metabolism, leading to hypocalcaemia, increased phosphate retention, and secondary hyperparathyroidism, all of which have detrimental effects on health (3). The condition previously referred to as renal osteodystrophy has been redefined as chronic kidney disease – mineral & bone disorder (CKD-MBD). This disorder encompasses abnormalities in bone formation, volume, and strength along with laboratory changes in vitamin D, Parathyroid hormone (PTH), calcium, or phosphorus leading to calcification in blood vessels and soft tissues (4). In addition to impaired kidney function CKD leads to iodine retention, metabolic acidosis, and proteinuria contributing to changes in thyroid function (5). Recent research exploring the relationship subclinical hypothyroidism and CKD and vice versa has garnered attention for its potential to prevent cardiovascular complications. Notably, the alterations in thyroid levels and bone mineral profiles have been primarily investigated in CKD stages G3a-G5 (with a GFR less than 60 mL/min). However, literature addressing these changes in the early stages of CKD (G1 and G2, where GFR exceeds than 60 mL/min) remains limited.

This study hypothesizes that individuals in the early stages of chronic renal disease, the majority of whom are not undergoing dialysis, will demonstrate variations in thyroid function and bone mineral profiles. Identifying these connections is vital, given that cardiovascular issues rank among the leading causes of mortality in CKD patients. The heart and kidneys interact at multiple levels, particularly when CKD arises as a complication of diabetes or hypertension, leading to hemodynamic interactions between the failing heart and the kidneys (6).

This study aims to conduct a retrospective analysis of Thyroid stimulating hormone (TSH) levels and markers of the bone mineral profile, including Vitamin D, PTH, calcium, phosphorus, magnesium, and alkaline phosphatase (ALP) in individuals diagnosed with early-stage CKD based on GFR.

## 2. MATERIALS AND METHODS

### 2.1. Patient and Ethical Approval

This retrospective cross-sectional study was conducted involving chronic kidney disease (CKD) patients within the nephrology department of Sri Ramachandra Medical College Hospital, Chennai, India from January to June 2022. The Study protocol was approved by the Institutional Ethics Committee, Sri Ramachandra Institute of Higher Education and Research (Ref.No-IEC-CSP/22/AUG/115/469) ensuring compliance with the institutional standard ethical guidelines. A waiver for written consent was obtained due to the study's retrospective design, and stringent measures were implemented to maintain patient confidentiality throughout the research process.

### 2.2. Data Collection and Methodology

Eligible participants included males and non-pregnant females aged over 18 years with a CKD diagnosis (n=247) diagnosed and received treatment at the nephrology department, Sri Ramachandra Medical College Hospital, Chennai, Tamilnadu between January to June 2022. The sample size was calculated to be 240, reflecting a 95% confidence interval and a 5% margin of error. Initially, data from 350 patients were selected based on the CKD diagnosis and laboratory records were reviewed retrospectively to gather baseline characteristics and laboratory data. Ultimately, 247 participants were included based on the completeness of the data available.

The study population was categorized into three groups according to the severity of CKD as defined by the estimated glomerular filtration rate (eGFR) in alignment with KDIGO criteria: Group1- CKD stage 1 (n=137) CKD diagnosed individuals with calculated eGFR more than 90 mL/min; Group2- CKD stage 2 (n=55) CKD diagnosed individuals with calculated eGFR 60 mL/min to 90 mL/min; and Group3- CKD stage 3-5 (n=57) CKD diagnosed individuals with calculated eGFR less than 60 mL/min.

### 2.3. Methodology for the biomarkers

The study analysed various parameters, including Vitamin D, Parathyroid hormone (PTH), calcium, magnesium, phosphorus, Thyroid Stimulating hormone (TSH), creatinine, and Alkaline phosphatase (ALP). eGFR

calculations were performed using an online calculator provided by CKD-EPI. All biomarkers were assayed on automated platforms, immunoassay markers evaluated using Cobas 8000 e602 (Roche, Basel, Switzerland), while routine chemistry markers were measured on the AU series (Beckman Coulter, CA, USA). Detailed methodologies for each biomarker can be found in Table 1.

**Table 1.** Data on biomarkers included in the study and their method of analysis with reference intervals

| Biomarker | Analyser | Method of Analysis | Sample used for analysis | Reference interval with units |
|---|---|---|---|---|
| Vitamin D | Roche Cobas | Electro Chemiluminescence Immunoassay | Serum | More than 30 ng/mL |
| TSH | Roche Cobas | Electro Chemiluminescence Immunoassay | Serum | 0.27-4.2 microIU/mL |
| PTH | Roche Cobas | Electro Chemiluminescence Immunoassay | Serum | 15-65 pg/mL |
| Calcium | Beckman Coulter AU Series | Arsenazo III | Serum | 8.8-10.6 mg/dL |
| Phosphorus | Beckman Coulter AU Series | Phosphomolybdate | Serum | 2.5-4.5 mg/dL |
| Magnesium | Beckman Coulter AU Series | Xylidyl blue | Serum | 1.8-2.6 mg/dL |
| Creatinine | Beckman Coulter AU Series | Modified Jaffe's | Serum | 0.7-1.1 mg/dL |
| Alkaline Phosphatase | Beckman Coulter AU Series | Para NitroPhenyl Phosphate-AMP Buffer | Serum | Less than 120 IU/L |

Notes: TSH- Thyroid stimulating hormone; PTH- Parathyroid hormone

## 2.4. Statistical Analysis

The data were statistically analysed using SPSS software version 20.0 (SPSS Inc., Chicago. IL, USA). The study population was stratified into three groups based on GFR: Group 1 (GFR > 90 mL/min); Group 2 (GFR 60-90 mL/min); Group 3 (GFR < 60 mL/min). Following the Kolmogorov-Smirnov test for normality, the data were presented as median values with interquartile ranges. Comparative analysis among the three groups was conducted using the Kruskal Wallis test, with a significance p-value of <0.05. Additionally, Spearman correlation analysis was performed to examine the relationships between the study variables.

# 3. RESULTS AND DISCUSSION

The analysis of the collected data indicated notable differences among the three groups classified based according to eGFR. Notably, 75% of the study participants were female, with baseline ages for the three groups recorded at 52.5, 68, and 66.5 years, respectively ($p < 0.001$). The variations in biomarker levels across the groups are detailed in Table 2, where statistically significant differences were observed in Vitamin D, creatinine, parathyroid hormone (PTH), and phosphorus levels. The prevalence of hypothyroidism among the three groups is illustrated in Figure 1, showing a significant increase, particularly in chronic kidney disease (CKD) patients with GFR of less than 60 mL/min ($p<0.05$).

As depicted in Figure 2, the participants were further categorized based on their vitamin D levels: sufficient (greater than 30 ng/mL), insufficient (20-30 ng/mL), and deficient (less than 20 ng/mL). A significant increase in the prevalence of vitamin D deficiency was identified across the three groups ($p < 0.05$). Subsequent correlation analyses assessed the effects of changes in GFR on the parameters included in the study. The findings presented in Table 3 reveal that only creatinine, Vitamin D, and PTH showed significant correlations, while phosphorus levels did not exhibit a correlation with changes in GFR. Table 3 Shows data from Spearman correlation analysis between GFR and other parameters in the study. The values are represented as correlation coefficients (rho($\boldsymbol{\rho}$)-values).

### 3.1. TSH Levels in Early Stages of CKD

Thyroid disorder in CKD, particularly hypothyroidism, are recognized as prevalent endocrine disorders. Initially, thyroid hormone deficiency was considered as a physiological aimed at minimizing protein loss and conserving metabolism during the advanced stages of CKD. Subsequent research has suggested a bidirectional relationship between thyroid function and kidney health. Hypothyroidism can lead to a reduction in tubular mass, cardiac output, renin-angiotensin-aldosterone system (RAAS) activity, and kidney-to-body weight ratio, all of which may adversely affect kidney function. Conversely, CKD can result in iodine retention, selenium deficiency, proteinuria, metabolic acidosis & uraemia which contribute to the development of hypothyroidism (5). Importantly, hypothyroidism in CKD has been identified as an under-recognized risk factor for cardiovascular complication, including endothelial dysfunction, impaired systolic function, and abnormal ventricular conduction. This relation has often been examined concerning triiodothyronine levels (7), while research by Kang *et al.* (9) posits that subclinical hypothyroidism with thyroid-stimulating hormone (TSH) levels exceeding 5 mIU/L is associated with impaired left ventricular function (8) and a 42% mortality rate at baseline.

**Table 2.** Data on the comparison of the parameters among the three groups and their statistical significance between the groups.

| | **Group 1 GFR > 90 Median (IQR) (n=135)** | **Group 2 GFR 60-90 Median (IQR) (n=55)** | **Group 3 GFR < 60 Median (IQR) (n=57)** | **P value*** |
|---|---|---|---|---|
| Age (Years) | 52.5 (23) | 68 (24) | 66.50 (17) | <0.001* |
| Creatinine (mg/dL) | 0.6 (0.53-0.67) | 0.9 (0.77-1.04) | 1.9 (1.27-5.07) | <0.001* |
| Vitamin D (ng/mL) | 23.04 (13.29-32.79) | 22.82 (13.42-32.22) | 14.80 (2.75-26.86) | <0.001* |
| Parathyroid Hormone (pg/mL) | 37.96 (22.27-53.65) | 37.14 (15.94-58.34) | 47.11 (8.31-85.91) | 0.010* |
| Alkaline Phosphatase (U/L) | 84 (60-108) | 82 (66-98) | 89 (62-116) | 0.064 |
| Calcium (mg/dL) | 9.3 (8.8-9.8) | 9.2 (8.5-9.9) | 9.1 (8.4-9.8) | 0.391 |
| Magnesium (mg/dL) | 2.0 (1.8-2.2) | 2.0 (1.8-2.2) | 1.9 (1.6-2.2) | 0.428 |
| Phosphorus (mg/dL) | 3.5 (2.8-4.2) | 3.7 (3.2-4.2) | 3.9 (3.4-4.4) | 0.018* |
| Thyroid Stimulating Hormone (µIU/mL) | 2.06 (0.37-3.75) | 3.15 (1.27-5.03) | 2.96 (0.35-5.57) | 0.103 |

Notes: GFR- Glomerular filtration rate; IQR- Interquartile range

**Table 3.** Spearman's rank correlation coefficient (GFR vs others parameters)

| | **Creatinine** | **Vitamin D** | **PTH** | **ALP** | **Calcium** | **Magnesium** | **Phosphorus** | **TSH** |
|---|---|---|---|---|---|---|---|---|
| GFR | 0.852** | 0.123* | 0.172** | 0.120 | 0.025 | 0.010 | 0.090 | 0.084 |

** Correlation (**ρ-values**) is significant at p<0.01. * Correlation (**ρ -values**) is significant at p<0.05. *p value <0.05 is considered statistically significant. PTH - parathyroid hormone; GFR- Glomerular filtration rate; ALP- Alkaline phosphatase; TSH- Thyroid stimulating hormone.

In light of these findings, our study aimed to explore the complexities of TSH levels in early non-dialysis CKD patients (9). Research by Lo *et al.* (10) established a significantly increased prevalence of hypothyroidism across all CKD stages, although a direct causal relationship was not established. In contrast, Trager *et al.* (11) found a significant association among CKD patients with subclinical autoimmune hypothyroidism. Furthermore, a study by Kim *et al.* (12) indicated that unresolved subclinical hypothyroidism is linked to a low three-year survival rate with an eGFR decline of approximately 14.4 mL/min annually.

Our study found that the prevalence of hypothyroidism significantly increased with the progression of CKD stages (Figure 1) which was consistent with the findings of the abovementioned studies. However, we did not establish a significant difference in TSH levels among the three groups analysed. The observed increase in hypothyroidism prevalence in CKD stages 1 and 2 may be attributed to the predominantly female population (75%) and the rising global prevalence of hypothyroidism influenced by changing food habits & sedentary lifestyles (13).

This observation aligns with the findings of Ansari *et al.* (14), in which suggested that despite substantial variations in patient proportions in the early stages of CKD, changes in TSH levels were insignificant in stages 1 and 2, with a marked increase occurring only after stage 3a. It is essential to recognize that TSH levels alone may not fully reflect the presence of hypothyroidism; low T4 levels could provide a more comprehensive assessment of the condition. Potential explanations for normal TSH levels, despite altered physiological mechanisms, include reduced activity of the hypothalamic-pituitary axis, decreased expression of TSH receptors in the hypothalamus, and an increased half-life of TSH (13,14). Furthermore, the lack of consideration regarding the duration of hypothyroidism and thyroid supplementation in CKD stage 3 may have influenced the significance of our results.

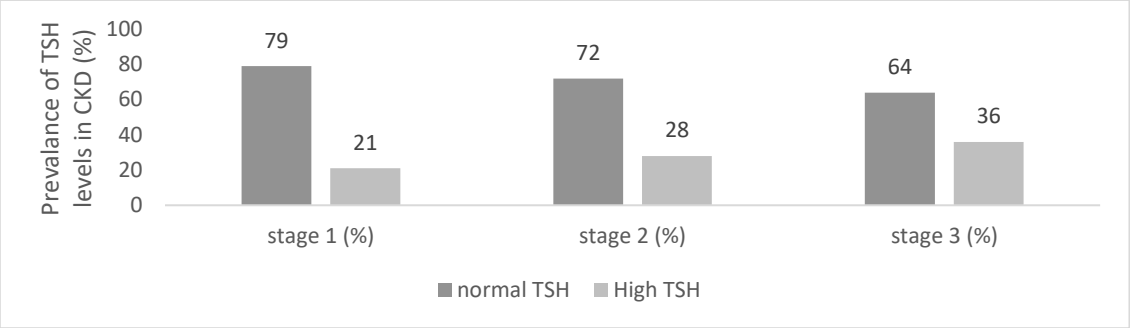


**Figure 1.** Bar graph showing comparison of prevalence of hypothyroidism (%) in three different groups included in the study ($p<0.05$). Y-axis represent percentage of the affected population and X axis represents the three stages of CKD as per the study group.

## 3.2. Bone Mineral Profile in Early Stages of CKD

Bone-related disorders exhibit a significant correlation with kidney pathology. The involvement of multiple markers in the assessment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) has been a subject of ongoing discussion. To address this issue and enhance understanding of the associated complications and extra skeletal effects, renal osteodystrophy was redefined as trifactorial CKD-MBD by KDIGO 2005. Although this guideline designates bone biopsy as the gold standard for diagnosis, practical challenges have prompted reliance on routine markers, including vitamin D, PTH, calcium, phosphate, magnesium & ALP for diagnosis, treatment, and prognosis of CKD-MBD (15). The revised KDIGO guidelines of 2017 further emphasize the importance of these markers, especially in the early stages of CKD, relevant to patients who are not yet on dialysis or are in the early stages of dialysis.

The primary consequences of CKD-MBD encompass vitamin D deficiency, secondary hyperparathyroidism (SHPT), hypocalcaemia, and hyperphosphatemia. These conditions can lead to soft tissue, vascular calcification, and its related cardiovascular complications (16). Our study illustrates a statistically significant increase in the prevalence of vitamin D deficiency, accompanied by a decrease in adequate Vitamin D levels among CKD patients as shown in Figure 2.

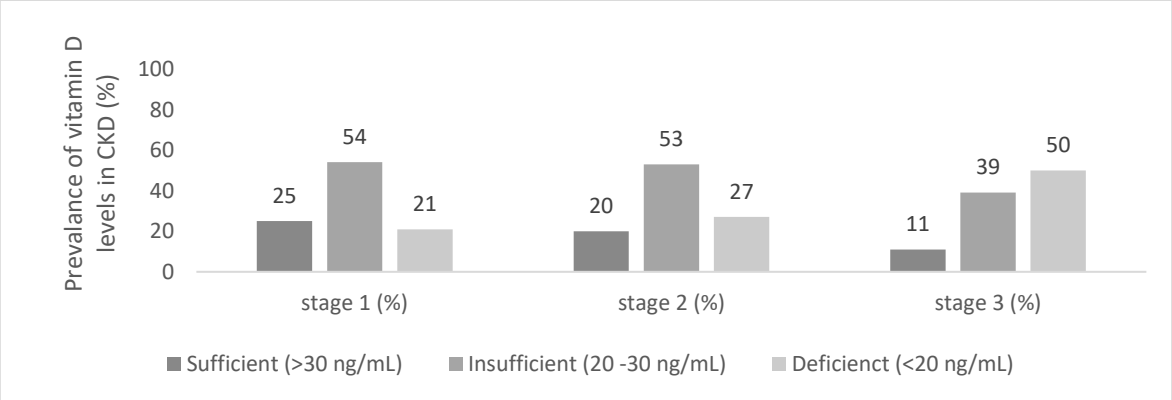


**Figure 2.** Bar graph showing comparison of prevalence of Vitamin D status (%) in three different groups included in the study ($p<0.05$). Y-axis represent the percentage of the affected population and X axis represents the three stages as per the study group; each group is further subdivided based on Vitamin D status as Sufficient- more than 30 ng/mL; Insufficient- 20-30 ng/mL; Deficient – less than 20 ng/mL.

Vitamin D (Vit D) is a well-recognised prohormone, frequently discussed due to the variability in diagnostic guidelines and treatment recommendations. Research by Navaneethan *et al.* (17), indicates that maintaining Vit D levels above 15 ng/mL may reduce mortality risk. Additionally, studies presented by Molina *et al.* (18) demonstrate associations between vitamin D deficiency and various adverse outcomes, including cardiovascular disease, albuminuria, renal disease progression, vascular calcification, and left ventricular hypertrophy. Our study revealed a statistically significant difference in vitamin D levels ($p<0.001$) and a significantly elevation in PTH levels ($p=0.010$) across the three studied groups. These findings are already confirmed by existing literature, particularly in patients with a GFR below 60 mL/min.

The unique aspect of this study is its focus on the alterations in Vit D and PTH levels during the early stages of CKD aligning with study conducted by Serena Torres *et al.* (19). A comprehensive review by Franca *et al.* (20), indicates that vitamin D levels begin to decline at stage 2 of CKD, which is consistent with our findings and holds implications for the prognosis of secondary hypoparathyroidism.

The relationship between PTH and Vit D possesses significant historical importance, In 1970, Bricker and Slatopolsky proposed a 'trade-off hypothesis' concerning the development of SHPT, suggesting that PTH levels may be adjusted to maintain phosphate levels (21). This theory was later refined with the discovery of Fibroblast growth factor 23 (FGF 23), which indicates that FGF23 levels begin to rise in the early stages of chronic kidney disease (CKD), often before observable changes in PTH and phosphate levels occur (22). FGF 23 increases during the initial phases of renal dysfunction through two primary mechanisms. The first mechanism involves enhanced phosphate excretion via transporters in the proximal convoluted tubule. The second mechanism entails a reduction Vitamin D synthesis by inhibiting the activity of 1-alpha hydroxylase. As a result, FGF 23 effectively mitigates hyperphosphatemia but at the expense of decreasing vitamin D levels, potentially initiating SHPT (23). The triad of low calcium, low vitamin D, and hyperphosphatemia can lead to SHPT and its related complications. Consequently, during the early stages of CKD, vitamin D levels are observed to decrease while PTH levels increase. In terms of additional bone mineral profiles, phosphorus levels were significantly elevated among the three groups ($p=0.018$); however, this correlation did not manifest in the analysis conducted.

This lack of correlation may be attributed to the fact that the majority of patients demonstrated sufficient levels of vitamin D in stages 1 and 2 of CKD, which may be too early to expect a definitive correlation between phosphate levels and GFR. This explanation may also account for the insignificant difference in calcium levels observed among the three groups ($p=0.391$). The KDIGO 2017 recommendations advocate for annual monitoring of alkaline phosphatase (ALP) levels in patients with CKD-MBD. Numerous studies have identified bone-specific ALP as a reliable marker for bone turnover, indicating that the high incidence of adynamic bone disease within the dialysis population may have affected the significance of our findings across the three groups ($p=0.064$) (23-28).

### 3.3. Limitations and future scope

The small sample size and the limited history related to supplementations are notable limitations that hinder the establishment of causality for the findings and necessitate careful interpretation. Consequently, a follow-up study involving a larger and more diverse population is essential to validate these findings, considering geographical, demographic, ethnic, and genetic variability. Moreover, future research should incorporate the examination of comorbidities such as hypertension and diabetes mellitus, as well as molecular markers including FGF 23, sclerostin, and klotho levels, to enhance the assessment of early stages of CKD-MBD.

## 4. CONCLUSIONS

This study concludes that alterations in vitamin D followed by PTH represent the earliest biomarkers for evaluating CKD-MBD in its initial stages, occurring prior to any changes in calcium and phosphate levels. While, ALP is a non-specific biomarker, annual assessments can be useful for diagnosing adynamic bone disease. Additionally, the findings indicate a higher prevalence of hypothyroidism in the early stages of CKD than previously reported in the literature. Therefore, diligent monitoring, along with appropriate supplementation of vitamin D and thyroid hormones at the correct stage, may assist in preventing the progression of renal disease and reducing the associated risk of cardiovascular disease.

**Author contributions:** IRR, EK, SS: Conceptualization, Methodology, Material preparation, Data collection, Formal analysis and investigation, writing-original draft preparation, Review and editing, Resources and supervision. KS & KSS: Conceptualization, Methodology, writing-original draft preparation, Review and editing, Resources and supervision.

**Funding:** No funding was received to assist with the conduct of this study and preparation of this manuscript.

**Acknowledgements**: The authors would like to acknowledge Dr.R.Janani, Senior Resident, Department of Biochemistry for support in statistical analyses.

**Ethics statement:** The study was approved by Sri Ramachandra Institute of Higher Education and Education, The Institutional Ethical Committee - (UG & Non-Med.PG students), (CSP/22/AUG/115/469, Date: 30.08.2022).

**Conflict of interest:** The authors declare that there is no conflict of interest concerning this study.

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