

Predictive Modeling for the Diagnosis of Chronic Kidney Disease-Mineral and Bone Disorder Using Biochemical and Bone Turnover Markers

Hussein Bahaa Abd Alrzaaq¹, Ali Mohammed Kadhim², Mustafa Hameid Salim³, Anwer Nageh AL-Hatemy⁴

¹Department of Physiology, Faculty of Medicine, Jabir Ibn Hayyan University for Medical and Pharmaceutical Sciences, Najaf, Iraq

²Department of Biochemistry, Faculty of Medicine, Jabir Ibn Hayyan University for Medical and Pharmaceutical Sciences, Najaf, Iraq

³Department of Medical Laboratories, AL Najaf Health Directorate, Najaf, Iraq

⁴Department of Imam Ja'far al-Sadiq University, Najaf Branch. College of Medical and Health Technology, aesthetics, Najaf, Iraq

Abstract— *Background: Disruptions in mineral metabolism, bone turnover, and hormone regulation are hallmarks of chronic kidney disease-mineral and bone disorder (CKD-MBD), a frequent consequence of CKD. Aim: The purpose of this study was to assess biochemical anomalies in CKD-MBD patients as well as the diagnostic efficacy of CTX and a multivariable prediction model. Methods: Eighty-eight CKD-MBD patients and eighty-eight healthy controls participated in the study. Phosphate, calcium, PTH, urea, creatinine, vitamin D, and C-telopeptide (CTX) serum levels were compared between the groups. ROC curve analysis was used to evaluate diagnostic performance. Results: When compared to controls, CKD-MBD patients had considerably higher levels of PTH, CTX, urea, and creatinine and significantly lower levels of calcium and vitamin D. CTX demonstrated reasonable diagnostic performance (AUC = 0.71, sensitivity = 78.0%, specificity = 64.0%) and was considerably higher in patients. Compared to CTX alone, the multivariable model performed better (AUC = 0.89, sensitivity = 86.0%, specificity = 82.0%, accuracy = 84.0%). The most significant predictors were PTH, creatinine, CTX, and urea. Conclusion: patients with CKD-MBD show notable abnormalities in bone turnover, vitamin D status, mineral metabolism, and renal function. When it comes to diagnosing CKD-MBD, a multivariable model outperforms CTX alone.*

Keywords— Chronic kidney disease, bone changes, artificial intelligence.

I. INTRODUCTION

A major global public health issue, chronic kidney disease (CKD) is linked to high rates of morbidity and mortality. Among its sequelae, skeletal fragility, arterial calcification, and cardiovascular disease are all exacerbated by abnormalities in mineral and bone metabolism, which are together referred to as CKD-mineral and bone disorder (CKD-MBD) [1][2]. abnormalities in bone turnover, which reflect changes in osteoclastic and osteoblastic activity as well as changes in hormonal and biochemical regulators of bone remodeling, first appear early in chronic kidney disease (CKD) and worsen as kidney function declines.

Numerous indicators are involved in the intricate pathophysiology of bone turnover in CKD. Since its elevation in secondary hyperparathyroidism promotes greater bone resorption and turnover, parathyroid hormone (PTH) continues to be the primary indicator of bone turnover; on the other hand, abnormally low PTH levels are linked to adynamic bone disease) [3]. C-terminal telopeptide of type I collagen (C-telopeptide, CTX), a marker of bone resorption, provides more information about osteoclastic activity and could improve the evaluation of bone dynamics) [4].

Mineral imbalances are also important: phosphorus (P) tends to build up because of decreased renal clearance, which leads to hyperphosphatemia and stimulates PTH release, while serum calcium (Ca) may decrease because of decreased

intestinal absorption and poor vitamin D metabolism) [5]. Early in chronic kidney disease (CKD), decreased 1 α -hydroxylase activity reduces the active form of vitamin D, 1,25-dihydroxyvitamin D (calcitriol), aggravating hypocalcemia and secondary hyperparathyroidism) [6].

In the meantime, increased serum urea and creatinine, which are indicators of deteriorating renal function, indicate decreased calcitriol synthesis and impaired phosphorus clearance, which indirectly signals the onset of CKD-MBD) [7]. PTH, CTX, calcium, phosphorus, 1,25-dihydroxyvitamin D, urea, and creatinine are all indicators of bone turnover in chronic kidney disease (CKD) that work together to offer a thorough biochemical evaluation and direct clinical treatment.

Understanding and following these recommendations is essential for improving bone health, preventing fractures, and reducing mortality in CKD patients. A number of biochemical markers can now be incorporated into standard prediction models thanks to recent advancements in machine learning and artificial intelligence. This could improve the early identification and categorization of hazards in chronic diseases, such as CKD-MBD) [8].

II. MATERIALS AND METHODS

2.1. Study Participants and Sample Collection:

All participants had fasting blood samples taken between 8:00 and 10:00 AM to minimize circadian variation in metabolic markers. Venous blood was collected into

appropriate tubes: EDTA tubes for C-telopeptide (CTX) and serum separator tubes for calcium, urea, creatinine, parathyroid hormone (PTH), and 1,25-dihydroxy vitamin D3 measurements.

Samples were centrifuged at $1500\text{--}2000 \times g$ for 10–15 minutes after clotting at room temperature (for serum). Serum or plasma supernatants were aliquoted and stored at -80°C until analysis.

2.2. Biochemical Assays

2.2.1. C-telopeptide (CTX)

Plasma CTX levels were measured using a commercially available ELISA kit (IDS) according to the manufacturer's instructions. Absorbance was measured at the recommended wavelength and concentrations were calculated using a standard calibration curve.

2.2.2. Calcium (Ca)

Serum total calcium was measured using an automated chemistry analyzer (Beckman Coulter AU 400) based on the o-cresolphthalein complexone method.

2.2.3. 1,25-dihydroxy Vitamin D3

Serum $1,25(\text{OH})_2\text{D}_3$ levels were measured using a competitive immunoassay kit (DiaSorin) on an automated analyzer (Beckman Coulter Access 2).

2.2.4. Parathyroid Hormone (PTH)

Intact PTH was measured using a chemiluminescent immunoassay (Beckman Coulter Access 2).

2.2.5. Serum Urea

Urea was measured enzymatically using the urease–glutamate dehydrogenase method on an automated analyzer (Beckman Coulter AU 400).

2.2.6. Serum Creatinine

Serum creatinine was measured using an enzymatic method or Jaffe reaction on Beckman Coulter AU 400 analyzer.

2.3. Ethical Approval and Informed Consent

The study was conducted in accordance with the Declaration of the World Medical Association (WMA). Ethical approval was obtained from the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrollment.

2.4. Statistical Analysis

Data were analyzed using SPSS version 16 and Microsoft Excel 2010. Continuous variables were expressed as mean $\pm$ standard deviation. Independent t-test was used for comparison between groups, and chi-square test was used for categorical variables. A p -value < 0.05 was considered statistically significant.

2.5. Machine Learning and Predictive Modeling

The combined predictive performance of biochemical predictors in CKD-MBD was assessed using a supervised machine learning-based approach in addition to traditional statistical analysis.

In as well as demographic parameters (age and gender), a multivariable dataset was created that included CTX, PTH, calcium, phosphate, urea, creatinine, and 1,25-dihydroxyvitamin D3. Binary classification (CKD-MBD

patients vs. controls) was used to define the outcome variable.

A logistic regression model was used as the major predictive model to determine the likelihood of illness presence based on combined biomarker profiles. This model was chosen because it is interpretable and appropriate for clinical decision support. A random forest model was also used to measure comparative performance.

The model outputs, expressed as predicted probabilities, were analyzed using receiver operator characteristics (ROC) curves.

Internal validation was carried out with five-fold cross-validation to assure durability. Feature contribution was measured using Random Forest feature significance ratings and standardized regression coefficients (logistic regression).

The area under the ROC curve (AUC) was used to evaluate discriminative performance, and model calibration was used to measure agreement between projected probability and observed outcomes. Using the Youden index, sensitivity and specificity were computed at ideal cutoff values.

To ascertain the additional diagnostic utility of the integrated machine learning approach, the performance of the multivariable predictive model was contrasted with single biomarker analysis (CTX alone).

III. RESULT

3.1. Study of biochemical parameters in patient and control:

The mean levels in the blood of PO4, Ca, and PTH in CKD-MBD patients are displayed in Figure 1 in comparison to the control group. Compared to controls, the patient groups mean PO4 level was lower (3.80 vs. 4.97 mg/dL), and this difference was statistically significant ($p < 0.05$). Additionally, patients' serum calcium levels were considerably lower than those of controls (7.30 vs. 9.01 mg/dL; $p < 0.05$). PTH, on the other hand, was much greater in CKD-MBD patients than in controls (102.50 vs. 48.78 pg/mL), with a statistically significant difference ($p < 0.001$). These results show that mineral metabolism in CKD-MBD patients is clearly disturbed.

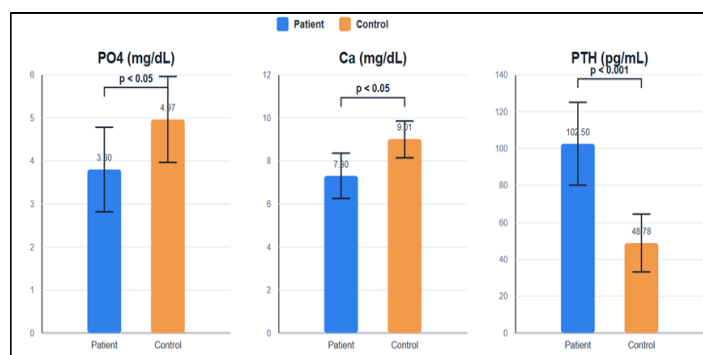


Fig. 1. The Total mean concentration of biochemicals (PO4, Ca and PTH) in CKD–mineral and bone disorder (CKD-MBD) patients in comparison with control group.

The mean serum urea and creatinine concentrations in CKD-MBD patients are compared to the control group in Figure 2. Compared to controls, the sick group's mean urea level was considerably higher (87.74 vs. 42.20 mg/dL; $p <$

0.001). Similarly, patients' blood creatinine levels were significantly higher than controls' (3.59 vs. 0.82 mg/dL; $p < 0.001$). These findings show that as compared to healthy controls, CKD-MBD patients had considerably worse renal function.

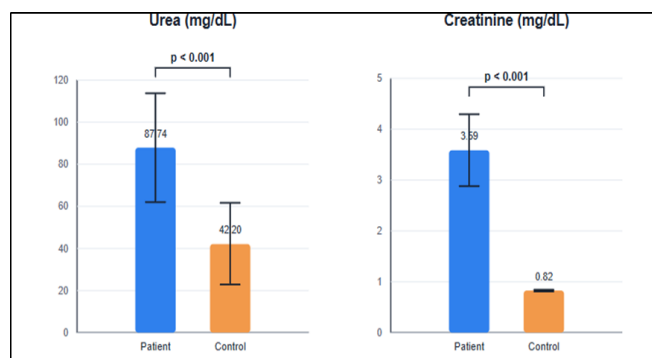


Fig. 2. The Total mean concentration of biochemicals (Urea and Creatinine) in CKD-mineral and bone disorder (CKD-MBD) patients in comparison with control group.

The mean levels of C-telopeptide and vitamin D in CKD-MBD patients are compared to the control group in Figure 3. Patients had considerably lower levels of vitamin D than controls (10.25 vs. 32.47 pg/mL; $p < 0.001$). On the other hand, patients had considerably greater levels of C-telopeptide than controls (0.89 vs. 0.35 ng/mL; $p < 0.001$). These findings show that CKD-MBD patients have a significant vitamin D deficit and elevated bone resorption activity.

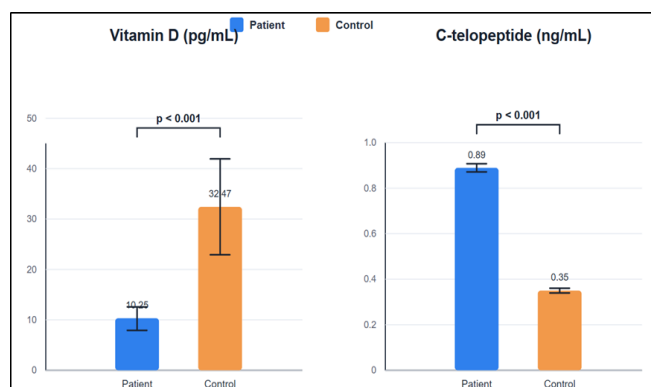


Fig. 3. The Total mean concentration of biochemicals (Vitamin D and C-telopeptide) in CKD-mineral and bone disorder (CKD-MBD) patients in comparison with control group.

The mean PO₄, Ca, and PTH concentrations in CKD-MBD patients are displayed in Figure 4 in comparison to controls for all age groups. In the 31–40 and 41–50 year age groups, PO₄ levels were substantially higher in patients than controls ($p < 0.05$), but there was no significant difference ($p > 0.05$) in the 51–60 year age group.

In every age group, patients serum calcium levels were considerably lower than controls ($p < 0.05$). PTH levels, on the other hand, were considerably greater in patients than in controls in every age group ($p < 0.001$).

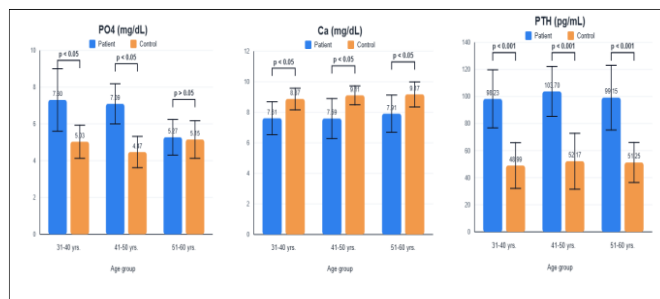


Fig. 4. The Mean concentration of biochemicals (PO₄, Ca and PTH) in CKD-mineral and bone disorder (CKD-MBD) patients in comparison with control group among age groups.

Figure 5 displays the average urea and creatinine concentrations across various age groups. In all age categories (31–40, 41–50, and 51–60 years), urea level was pointedly higher in CKD-MBD patient than in control ($p < 0.001$). Patients exhibited pointedly higher creatinine levels compared to controls across all age groups ($p < 0.001$). Irrespective of age, these results show that CKD-MBD patients have reduced renal function.

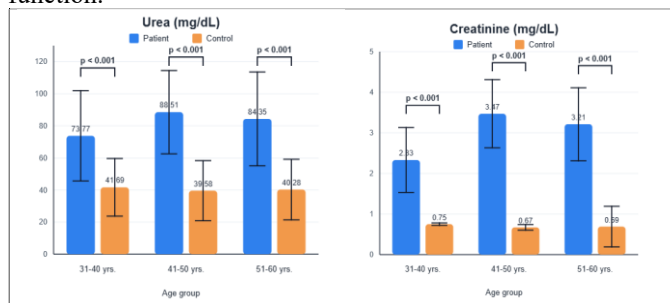


Fig. 5. The Mean concentration of biochemicals (Urea and Creatinine) in CKD-mineral and bone disorder (CKD-MBD) patients in comparison with control group among age groups.

Figure 6 shows an average concentration of C-telopeptide and 1,25-dihydroxyvitamin D₃ among age groups. In all age groups, patients with CKD-MBD shown considerably lower vitamin D₃ concentrations than control ($p < 0.001$).

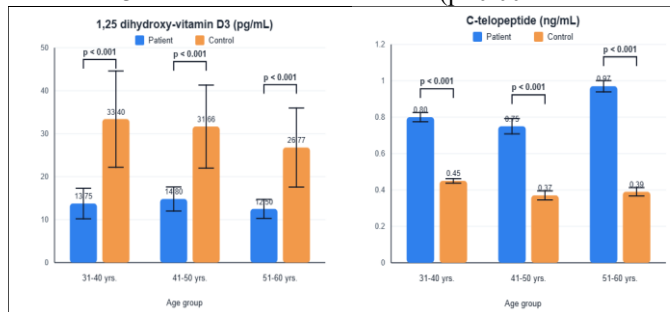


Fig. 6. The Mean concentration of biochemical (Vitamin D and C-telopeptide) in CKD-mineral and bone disorder (CKD-MBD) patients in comparison with control group among age groups

On the other hand, across all age categories, C-telopeptide levels were considerably greater in patients than in controls (p

< 0.001). These findings reveal the CKD-MBD participants of all ages had reduced levels of vitamin D and increased bone resorption activity.

The distribution of sex of CKD-MBD participants is shown in Figure (7). Males made up 43.0% of the overall sample, and females made up 57.0%. There were 88 patients in all, with a male to female ratio of 1:1.32. This suggests that in the community under study, CKD-MBD was more common in women than in men.

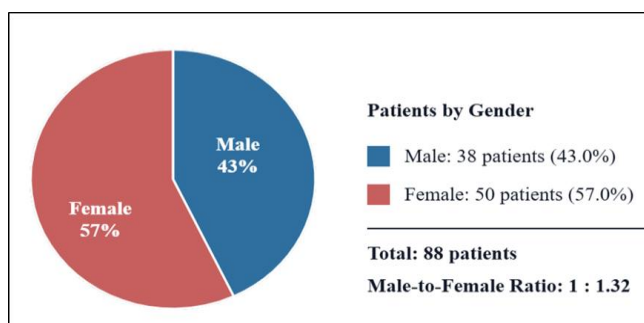


Fig.7. The percentages of CKD-mineral and bone disorder (CKD-MBD) patients among genders.

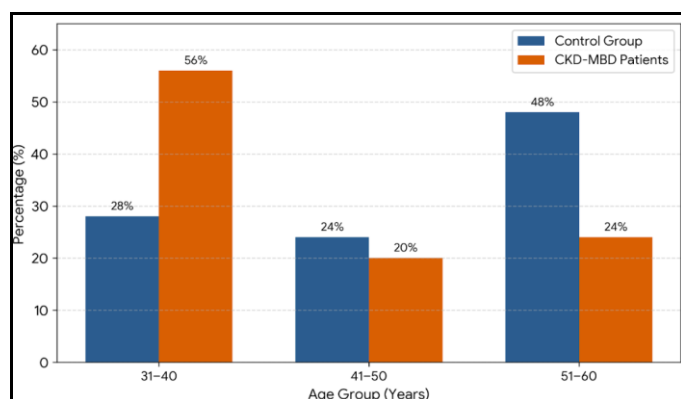


Fig. 8. The age distribution of the patient and control groups

The age distribution of the patient and control groups is displayed in Figure 8.

The age group of 51–60 years old had the largest percentage in the control group (48%), followed by 31–40 years old (28%) and 41–50 years old (24%). On the other hand, the age group of 31–40 years old had the largest percentage of CKD-MBD patients (56%), followed by 51–60 years old (24%) and 41–50 years old (20%). These findings show that, in comparison to controls, CKD-MBD patients were more concentrated in the younger age range of 31–40 years.

The study's suggested analytical approach is shown in Figure 9. Fasting blood specimens were used to assess biochemical indicators like CTX, PTH, phosphate, calcium, urea, creatinine, and 1,25-dihydroxyvitamin D₃. Following processing, the finished dataset was comprised into a supervised machine learning basis. To estimate the likelihood of CKD-MBD, a multivariable predictive model was created. ROC curve analysis and comparative diagnostic evaluation against single biomarker analysis were used to assess the

model's effectiveness.

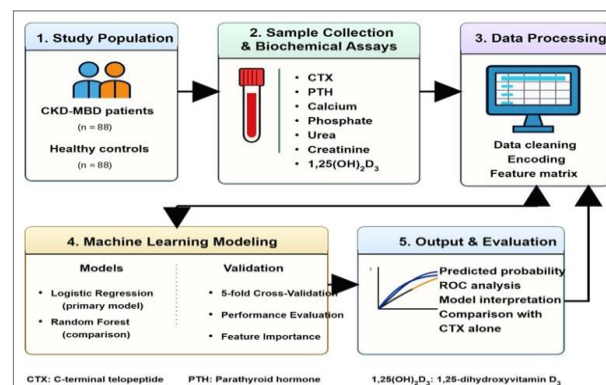


Fig. 9. Study workflow and machine learning pipeline (conceptual framework)

The receiver operating characteristic (ROC) analysis of C-terminal telopeptide (CTX) as a single diagnostic marker is shown in Figure 10. CTX demonstrated a small degree of biased power when it came to separating CKD-MBD patients from controls, indicating subpar solo diagnostic performance.

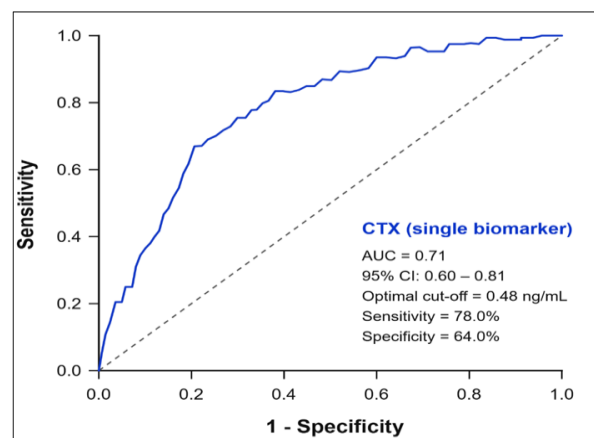


Fig. 10. Diagnostic performance of CTX as a single biomarker.

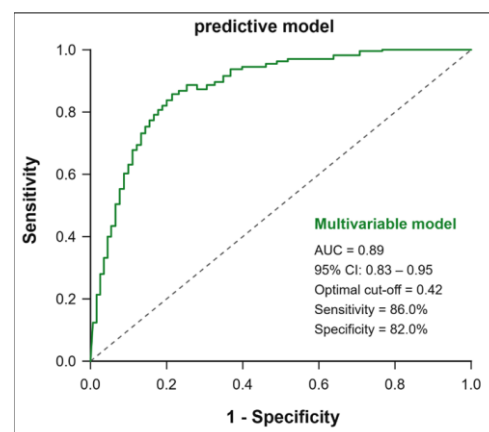


Fig. 11. Multivariable predictive model performance

Figure 11 displays the ROC curve of the multivariable prediction model depending on the combination biochemical results (CTX,PTH,calcium, phosphate,urea,creatinine, and

vitamin D-3). By improving the ability to distinguish between CKD-MBD patients and controls, the model shows better diagnostic performance than single biomarker analysis.

The ability to diagnose of CTX alone and the multivariable prediction model is compared in Figure 12. Better classification accuracy is shown by the combined model, highlighting the benefits of incorporating several biochemical markers into a machine learning system.

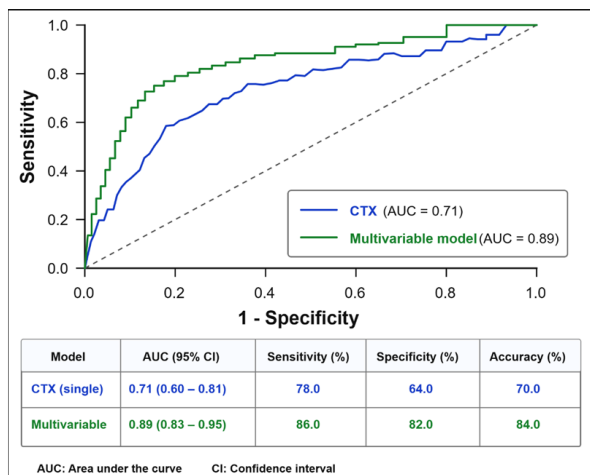


Fig. 12. Comparative diagnostic performance (CTX vs multivariable model),

Figure 13 displays relative contribution of every biochemical parameter in the multivariable model. The most predictions are expected to be PTH, creatinine, and CTX, followed by vitamin D3, calcium, and phosphate.

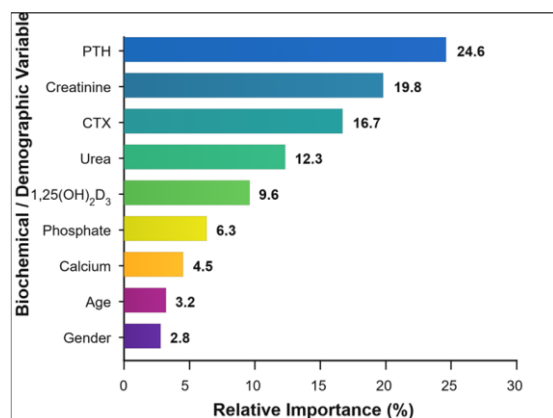


Fig.13. Biomarker contribution in predictive modeling

the figure 14, which illustrates the variations in bone turnover indicator expression between CKD-MBD patients and control subjects, displays the distribution pattern of CTX levels among study groups.

3.2. Machine learning-based diagnosis performance

A multivariable predictive framework was developed using CTX, PTH, calcium, phosphate, urea, creatinine ,1,25-dihydroxyvitamin D3, age, gender, and other chemical and demographic factors. The model generated a continuous estimated probability for CKD-MBD categorization.

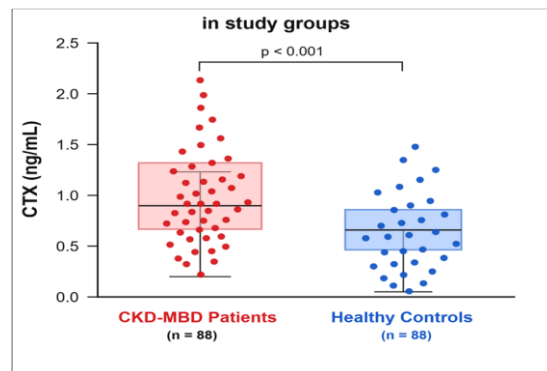


Fig.14. Distribution of CTX levels

The analysis of receiver operating characteristic (ROC) of the predicted probability shown superior diagnostic performance in comparison to single biomarker analysis. The multivariable model showed improved discrimination between CKD-MBD patients as well as controls, indicating that an integrated biomarker approach is better than individual indicators for disease classification.

When in comparison to CTX alone, the machine learning-based model showed better overall classification efficacy and higher diagnosis accuracy. This illustrates how multivariable integration improves the prediction of CKD-MBD diagnosis.

3.3. Model interpretations and standard compared analysis

Feature integrate analysis revealed that PTH, creatinine, and CTX contributed the most to the prediction model, although calcium and phosphate contributed less individually.

A comparison among a single biological marker assessment and the multivariable model demonstrated that CTX alone had moderate diagnostic performance while integrated models significantly improved classification ability, supporting the clinical importance of a machine learning-based approach in CKD-MBD evaluation.

IV. DISCUSSION

The current study found specific biochemical anomalies in CKD-MBD patients compared to the control group, such as considerably lower levels of calcium and vitamin D, increased levels of PTH and C-telopeptide, and noticeably elevated levels of urea and creatinine.

These findings provide credence to the theory that CKD-MBD is a systemic disease characterized by abnormalities in hormone regulation, mineral metabolism, and bone turnover. This is in line with the KDIGO guideline, which considers abnormalities in calcium, phosphate, PTH, vitamin D, and bone turnover to be important indicators of CKD-MBD [9].

In line with the much lower calcium levels in CKD-MBD patients, [12]. Discovered that patients on hemodialysis had decreased calcium levels than healthy control subjects. This result may be explained by secondary hyperparathyroidism, low intestinal calcium absorption, and decreased renal synthesis of active vitamin D. Recent reviews [10,11]. state that declining renal function results in secondary hyperparathyroidism and upsets the calcium-phosphate balance.

Furthermore, the notable rise in PTH in CKD-MBD patients is in line with recent findings. secondary hyperparathyroidism as a substantial component of CKD-MBD, despite the 2023 review of current and developing CKD-MBD indicators stating that elevated PTH is a common result of declining renal function. Thus, secondary hyperparathyroidism in CKD-MBD patients is confirmed by the higher PTH level in our research [20].

Vitamin D was much lower in hemodialysis patients than in controls, according to study which found significantly reduced 1,25-dihydroxyvitamin D3 [12]. Furthermore, it is in line with recent studies of CKD-MBD that show reduced active vitamin D, a crucial mechanism in CKD-MBD, is the cause of hypocalcemia and elevated PTH [20].

The significantly higher concentrations of C-telopeptide in CKD-MBD patients in comparison with controls suggested increased bone resorption activity. This is in line with the results of Xie et al, [13], who discovered that markers of bone turnover, such beta-C-terminal telopeptide, were significantly higher in advanced CKD and positively linked with PTH. Therefore, the elevated C-telopeptide in the current study supports increased bone turnover and bone resorption in CKD-MBD patients.

Urea and creatinine levels were considerably higher in CKD-MBD patients than in controls, both overall and across age groups. The results of Bhuvaneswari et al, [14], who found that CKD patients had significantly greater urea and creatinine indicators than healthy controls, are in line with this. Additionally, it validates the results of Madhavan et al. (2024), who discovered that abnormal creatinine levels were common in CKD patients. These findings demonstrate reduced glomerular filtration and renal excretion of nitrogenous waste products.

Nevertheless, the aggregate comparison's phosphate finding somewhat contradicts other research. Total PO₄ was lower in CKD-MBD patients than controls in this research, while age-group analysis showed higher PO₄ in younger patient groups and no significant difference in the oldest group. Hemodialysis patients had significantly higher phosphate levels than controls. It also runs counter to the 2024 dialysis CKD-MBD phenotypic research, which discovered that a sizable portion of CKD-MBD patients had high phosphorus levels. This disparity may be caused by the use of phosphate binders, dietary phosphate restriction, dialysis timing, nutritional status, or changes in CKD stage.

The current research investigation found that a higher proportion of CKD-MBD patients were female. This outcome could be in line with several population-based CKD-MBD results where a sizable portion of the identified CKD groups were female.

Nevertheless, a male predominance among CKD patients, in contrast to other CKD-MBD investigations that revealed a larger percentage of men. These differences may result from differences in the etiology of the disease, regional risk factors, patterns of hospital attendance, or sample size [14].

The age distribution of the research showed that most patients were between the ages of 31 and 40. On the other hand, most CKD patients were in the 50–75 age range. This

disparity may be caused by variations in the research population, inclusion criteria, geographical factors, early start of CKD, or referral patterns in the present sample.

The ROC evaluation of CTX as a single biomarker showed a respectable diagnostic performance for distinguishing CKD-MBD patients from healthy control subjects, with an AUC of 0.71, sensitivity of 78.0%, and specificity of 64.0% at an optimum cut-off value of 0.48 ng/mL. This implies that although CTX is a useful diagnostic tool, it is not a very accurate diagnostic marker by itself. Beta-C-terminal telopeptide was significantly higher in advanced CKD and was connected to PTH and bone turnover markers [17]. also confirms the results of Jørgensen et al, who found that total CTX levels were higher in CKD patients than in normal control subjects [18].

The greater CTX levels in CKD-MBD patients are consistent with increased bone resorption and impaired bone turnover. This validates hypothesis that CKD-MBD is caused by abnormalities in bone turnover, mineralization [9]., and hormone regulation. According to recent evaluations, CKD-MBD is a systemic disorder that affects calcium and phosphate levels as well as bone remodelling and vascular issues [21].

However, the current study's modest CTX AUC also suggests that CKD-MBD state cannot be sufficiently described by CTX alone. This partially contradicts studies that highlight bone turnover markers as powerful indicators of bone remodelling since CTX may be affected by both true bone resorption and reduced renal clearance in CKD. the elevated total CTX level in CKD may be related to impaired renal clearance. Therefore, it is important to carefully interpret CTX elevation, especially in combination with other biochemical indications [22].

The multivariable prediction model outperformed CTX alone in terms of diagnostic performance, with an AUC of 0.89, sensitivity of 86.0%, specificity of 82.0%, and accuracy of 84.0%. This implies that combining CTX with other biochemical and demographic parameters improves the ability to distinguish CKD-MBD patients from normal controls. This result is in line with the findings of Li et al, [19]. who used machine learning-based biomarker identification for CKD-MBD and shown that biomarker panels performed better in training models than single markers with high AUC values. This supports the existing conclusion that a multivariable approach offers a more accurate diagnosis of CKD-MBD.

The comparative ROC curve provides more evidence of the multivariable model's greater performance over CTX alone. The increase in AUC from 0.71 to 0.89 shows that although CTX helps with diagnosis, its clinical utility increases when combined with indicators of renal function, mineral metabolism, and demography. This is consistent with study, which recommends that CKD-MBD be assessed utilizing a combined evaluation of calcium, phosphate, PTH, vitamin D, and related markers rather than relying only on one test result [9].

The biomarker contribution analysis showed that PTH had the highest relative relevance, followed by creatinine, CTX, urea, vitamin D, phosphate, calcium, age, and gender. PTH

dominance is in line with the pathophysiology of CKD-MBD as secondary hyperparathyroidism is one of the main hormonal abnormalities in the condition. Increased PTH was shown to be a prevalent outcome of declining kidney function in the 2023 assessment of novel and current CKD-MBD markers. Additionally, it confirms the results of study, who found a separate connection between PTH and markers of bone turnover as beta-CTX [17].

It is also anticipated that creatinine and urea would make a significant contribution to the prediction model because they are markers of impaired renal function. Another study discovered that CKD patients had significantly greater urea and creatinine indicators than healthy controls [14], are in line with this. It also confirms the results of other study, who discovered that abnormal creatinine was common in CKD patients. The importance of creatinine and urea in the model therefore supports the link between renal failure and CKD-MBD [15].

CKD-MBD patients exhibited significantly greater CTX levels than healthy controls, according to the CTX distribution plot ($p < 0.001$). This is in line with the ROC result and validates the role of CTX as a marker of increased bone resorption in CKD-MBD. This outcome is in line with other studies who demonstrated higher overall CTX levels in CKD compared to controls [17,18].

Nonetheless, several studies and recommendations are against using CTX as a stand-alone diagnostic marker. This suggests that the strong performance of the present multivariable model should ideally be validated by a larger independent cohort.

V. CONCLUSION

CKD-MBD patients showed significant biochemical abnormalities in comparison to controls, including elevated levels of PTH, CTX, urea, and creatinine and decreased levels of calcium and vitamin D. These abnormalities suggested secondary hyperparathyroidism, accelerated bone resorption, and impaired renal function. When it came to diagnosis, the multivariable model outperformed CTX, which had a moderate diagnostic value. A mixture of biochemical signs is typically more useful than a single indication for evaluating CKD-MBD.

ACKNOWLEDGMENT

No specific funding was received from governmental, commercial, or non-profit organizations for the conduct of this research.

REFERENCES

[1] Isakova T, Nickolas TL, Denburg M, et al. KDOQI US commentary on the 2017 KDIGO CKD-MBD guideline update. *Am J Kidney Dis*. 2017;70(6):737-751.

[2] Kidney Disease: Improving Global Outcomes (KDIGO). Chronic kidney disease-mineral and bone disorder: update and controversies. *Kidney Int*. 2024.

[3] Sprague SM. Management of bone disorders in kidney disease. In: *Endocrine Disorders in Kidney Disease: Diagnosis and Treatment*. Springer International Publishing; 2019:231-242.

[4] Cejka D, Wakolbinger-Habel R, Zitt E, et al. Diagnosis and treatment of osteoporosis in patients with chronic kidney disease: joint guidelines of the Austrian Society for Bone and Mineral Research (ÖGKM), the Austrian Society of Physical and Rehabilitation Medicine (ÖGPMR), and the Austrian Society of Nephrology (ÖGN). *Wien Med Wochenschr*. 2022;173(13-14):299-318.

[5] Evenepoel P, Cunningham J, Ferrari S, et al. Diagnosis and management of osteoporosis in CKD: a KDIGO controversies conference report. *Kidney Int*. 2021;99(2):221-235.

[6] Wolf M, Shah A. Vitamin D and the kidney: physiology and pathophysiology. *Semin Nephrol*. 2020;40(4):359-372.

[7] Palmer BF, Clegg DJ. Kidney-protective effects of SGLT2 inhibitors. *Clin J Am Soc Nephrol*. 2023;18(2):279-289.

[8] Krisanapan, P., Tangpanithandee, S., Thongprayoon, C., Pattharanitima, P., & Cheungpasitporn, W. (2023). Revolutionizing chronic kidney disease management with machine learning and artificial intelligence. *Journal of Clinical Medicine*, 12(8), 3018.

[9] KDIGO CKD-MBD Update Work Group. (2017). KDIGO 2017 Clinical Practice Guideline Update for CKD-MBD.

[10] Williams, M. J., White, S. C., Joseph, Z., & Hruska, K. A. (2023). Updates in chronic kidney disease-mineral bone disorder. *Frontiers in Physiology*.

[11] Current and Emerging Markers and Tools Used in the Diagnosis and Management of CKD-MBD in Non-Dialysis Adult Patients. (2023). *Journal of Clinical Medicine*.

[12] Kanbay, M., et al. (2021). FGF23, alpha-Klotho and vitamin D mediated calcium-phosphate metabolism in haemodialysis patients.

[13] Xie, D., Zhao, L., Wu, L., & Ji, Q. (2023). The levels of bone turnover markers and parathyroid hormone and their relationship in chronic kidney disease. *Clinical Chimica Acta*.

[14] Bhuvaneshwari, V. N., et al. (2023). Comparison of serum urea, salivary urea, and creatinine levels in pre-dialysis and post-dialysis patients. *Cureus*.

[15] Madhavan, H., et al. (2024). Sociodemographic features, serum urea, creatinine and BUN/creatinine ratio in CKD patients. *Global Journal of Health Science and Research*.

[16] Phenotypes of Mineral Bone Disorder in Chronic Kidney Disease in a Dialysis Population. (2024).

[17] Xie, D., Zhao, L., Wu, L., & Ji, Q. (2023). The levels of bone turnover markers and parathyroid hormone and their relationship in chronic kidney disease. *Clinical Chimica Acta*.

[18] Jørgensen, H. S., et al. (2022). Circadian rhythm of markers of bone turnover in patients with chronic kidney disease. *Bone Reports*.

[19] Li, Y., Lou, Y., Liu, M., et al. (2024). Machine learning based biomarker discovery for chronic kidney disease-mineral and bone disorder. *BMC Medical Informatics and Decision Making*, 24, 36.

[20] Williams, M. J., White, S. C., Joseph, Z., & Hruska, K. A. (2023). Updates in chronic kidney disease-mineral bone disorder. *Frontiers in Physiology*.

[21] Nitta, K., Hanafusa, N., Akiyama, K., Kawaguchi, Y., & Tsuchiya, K. (2023). Chronic Kidney Disease-Mineral and Bone Disorder, from Bench to Bedside. *Kidney and Dialysis*.

[22] Bhuvaneshwari, V. N., et al. (2023). Comparison of serum urea, salivary urea, and creatinine levels in pre-dialysis and post-dialysis patients. *Cureus*.

[23] Madhavan, H., et al. (2024). Sociodemographic features, serum urea, creatinine and BUN/creatinine ratio in CKD patients. *Global Journal of Health Science and Research*.