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Serum FGF-23 and Vitamin D Deficiency as Predictors of Metabolic Syndrome in Chronic Kidney Disease

Tazeen Shah [1], Arsalan Ahmed Uqaili [1], Saima Naz Shaikh [1], Salahuddin Shaikh Madni[2], Rizwan Channa[3], Hira Saeed Khan[3]

[1]Department of Physiology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan, [2]Department of Physiology, Isra University, Hyderabad, Sindh, Pakistan, [3] Department of Medicine & Physiology, Suleman Roshan Medical College, Tando Adam, Sindh, Pakistan.

ABSTRACT

Background: Chronic kidney disease (CKD) is closely linked to disruptions in mineral metabolism and a high prevalence of metabolic syndrome. This study explored the relationship between serum fibroblast growth factor 23 (FGF-23), vitamin D deficiency, and metabolic syndrome in CKD patients.

Methods: A cross-sectional study was conducted from June 2024 to December 2024 at Liaquat University of Medical and Health Sciences, Jamshoro. Using purposive sampling, 200 CKD patients aged 18 years or older were included. Serum FGF-23 and vitamin D levels were measured, and metabolic syndrome was defined using NCEP ATP III criteria. Data was analyzed via SPSS for measures of central tendency and correlation, with $p<0.05$ considered statistically significant.

Results: Among 200 participants, 196 (98%) had metabolic syndrome. Serum FGF-23 levels rose significantly with advancing CKD stages (Stage 1: 120.5 ± 50.6 pg/mL; Stage 5: 680.3 ± 90.4 pg/mL, $p<0.01$), while vitamin D levels decreased (Stage 1: 25.6 ± 4.2 ng/mL; Stage 5: 10.2 ± 2.3 ng/mL, $p<0.01$). FGF-23 showed a weak positive correlation with fasting glucose ($r=0.16$, $p=0.03$), and vitamin D negatively correlated with blood pressure ($r=-0.11$, $p=0.04$). Logistic regression identified elevated FGF-23 (OR=1.05, $p<0.01$), low vitamin D (OR=0.95, $p=0.02$), and older age (OR=1.06, $p<0.01$) as predictors of metabolic syndrome.

Conclusion: Metabolic syndrome was prevalent in 98% of CKD patients, primarily driven by elevated FGF-23 and vitamin D deficiency. Addressing these factors may help reduce cardiovascular risks and improve CKD outcomes.

Keywords: FGF-23, Vitamin D, Metabolic Syndrome X, Chronic Kidney Disease, Cardiovascular Diseases, Insulin Resistance.

Corresponding Author:
Dr. Arsalan Ahmed Uqaili,
Department of Physiology,
LUMHS, Jamshoro, Pakistan.
Email : arsalan.uqaili@lumhs.edu.pk
ORCID: https://orcid.org/0000-0003-3692-3707
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INTRODUCTION

Chronic kidney disease (CKD) is a global health challenge, progressing through multiple stages and affecting millions of individuals worldwide. The combined effects of mineral imbalances and metabolic disturbances in CKD patients pose significant treatment challenges, especially in regions like Pakistan, where healthcare services remain limited. Fibroblast growth factor 23 (FGF-23) has been identified as a key regulator of phosphate and vitamin D metabolism in CKD patients. Elevated serum FGF-23 levels are observed early in CKD progression, even before hyperphosphatemia becomes evident, and are associated with increased cardiovascular risk, insulin resistance, and metabolic dysfunction[1,2].

According to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, vitamin D deficiency exacerbates CKD-related complications and worsens disease progression[3]. Reduced 1 a-hydroxylase activity and enhanced FGF-23 production lead to distinct mineral and bone changes and promote systemic inflammation[4]. Research demonstrates that low vitamin D levels contribute to metabolic syndrome by inducing insulin resistance and elevating blood pressure and lipid levels[5]. However, the relationship between FGF-23 levels and vitamin D deficiency requires further investigation due to its significant role in promoting metabolic syndrome in CKD patients[6].

Patients with CKD frequently develop metabolic syndrome due to abdominal obesity, hypertension, dyslipidemia, and hyperglycemia, which exacerbate both kidney and cardiovascular complications[7]. This bidirectional relationship creates a vicious cycle, where metabolic syndrome accelerates CKD progression, and CKD further aggravates metabolic syndrome[8]. Osteocytes primarily produce FGF-23, which regulates phosphate homeostasis by reducing phosphate reabsorption and inhibiting vitamin D production[9]. As CKD advances, FGF-23 levels increase, leading to worse cardiovascular outcomes and higher mortality[10]. Studies reveal that elevated FGF-23 triggers metabolic syndrome through mechanisms involving insulin resistance and inflammation[11].

Research also shows that patients with vitamin D deficiency experience more pronounced metabolic syndrome symptoms when they have CKD[12]. Low vitamin D levels are linked to impaired glycemic control, weight gain, and elevated blood pressure, all of which contribute to metabolic syndrome[13]. The combination of vitamin D deficiency and elevated FGF-23 initiates a feedback loop that worsens kidney disease and elevates cardiovascular risk[14].

The prevalence of CKD in Pakistan is rising rapidly, primarily due to increasing rates of diabetes and hypertension, coupled with delayed diagnosis and treatment[15]. There is a paucity of data from South Asia, including Pakistan, regarding the interplay between FGF-23, vitamin D deficiency, and metabolic syndrome[16]. Understanding these relationships within the local context is crucial for developing effective management strategies tailored to the regional population[17]. The study aimed to assess the correlation between serum FGF-23, vitamin D deficiency, and metabolic syndrome in CKD patients. It will analyze demographics, metabolic syndrome frequency, and biochemical variations across CKD stages. The relationship between FGF-23, metabolic markers, and vitamin D decline will be examined, with correlation analysis identifying significant associations. Multivariable regression will determine predictors of metabolic syndrome, providing insights into CKD-related metabolic dysfunction for improved clinical management.

METHODS

This cross-sectional study was conducted at Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, Pakistan, targeting CKD patients seen in the nephrology outpatient clinic or admitted to the nephrology ward between June 2024 and December 2024. Approval for the study was obtained from the Research Ethical Committee of LUMHS, letter no 401249 dated 19 th December 2024. Adults (≥18 years) with CKD stages 3A to 5D (GFR ≤60 mL/min/1.73m²) were included. Patients were excluded if they had acute kidney injury (AKI) within the last three months, active infections, malignancies, or recent use of vitamin D supplements or phosphate binders, to minimize potential confounding factors.

A total of 200 participants were recruited using purposive sampling. The sample size was calculated using the formula [18].

$$n = \dfrac{Z^2\cdot p \cdot (1 – p)}{d^2 }$$

n = Required sample size

Z = Z-score corresponding to the desired confidence level (1.96 for 95% confidence)

p = Expected prevalence (50% for maximum sample size)

d = Margin of error (5%)

Thus, a sample size of 422 participants was initially calculated, but based on resource availability and clinical setting, 200 participants were recruited for this study.

Data collection included interviews, clinical assessments, and laboratory tests, supplemented by electronic health records. Demographic and clinical data (age, gender, BMI, socioeconomic status, CKD stage, duration of illness, comorbidities, and medications) were gathered through self-administered questionnaires. Fasting blood

samples were analyzed for serum FGF-23 (using ELISA) and 25-hydroxyvitamin D (using CLIA). Additional tests included fasting glucose, lipid panel, calcium, phosphate, and parathyroid hormone levels.

Modified NCEP ATP III criteria defined metabolic syndrome through its three or more components that included abdominal obesity with waist circumference measurements at ≥102 cm for men and ≥88 cm for women along with triglycerides at ≥ 150 mg/dL and low HDL under 40 mg/dL for men and 50 mg/dL for women and blood pressure at ≥ 130/85 mmHg or antihypertensive use and fasting glucose at ≥100 mg/dL or antidiabetic therapy.
Data was analyzed using SPSS 26.0. The data analysis included continuous variables presented as mean ± standard deviation, while categorical data appeared as frequencies and percentages. Serum FGF-23 and vitamin D correlations with metabolic syndrome components were evaluated through Spearman or Pearson analyses. Independent samples t-tests revealed mean differences between distinct groups, whereas ANOVA showed differences across CKD stages. All reported p values in this study needed to reach at least $p<0.05p < 0.05p<0.05$ levels of significance.

RESULTS

All participants provided written informed consent before the research and the data received complete anonymization. The analysis within this study respected all ethical guidelines established by the Declaration of Helsinki. The results obtained from this study will show the relationship between elevated FGF-23 levels and vitamin D deficiency alongside metabolic syndrome and their effects on chronic kidney disease progression to support effective patient care.

The measured FGF-23 serum levels spanned from 33.6 pg/mL to 797.6 pg/mL with a mean of 407.7 ± 223.5 pg/mL, which indicated significant variation based on the stage of CKD. A vitamin D deficiency appeared in 72% of participants, with their mean levels measured at 17.8 ± 7.4 ng/mL. The data in Table 3 demonstrates that FGF-23 mean levels grew substantially as patients moved through different stages of CKD ($p<0.01$) while showing a decreasing pattern of vitamin D mean levels. The patients identified with Stage 5 CKD exhibited the maximum average FGF-23 levels of 680.3 ± 90.4 pg/mL, although patients in Stage 1 possessed the least FGF-23 levels of 120.5 ± 50.6 pg/mL. Participants experiencing Stage 5 KD experienced the most significant decrease in vitamin D levels, which reached a minimum of 10.2 ± 2.3 ng/mL in this stage. A weak positive link exists between FGF-23 serum levels and fasting glucose measurements ($r=0.16$, $p=0.03$) thus suggesting FGF-23 plays a part in glucose regulation dysfunction. No correlations existed between FGF-23 levels and body mass index measurements, along with fasting triglycerides. The analysis showed a relationship between lower vitamin D levels and blood pressure elevation as well as BMI increase at a weak intensity ($r=-0.11$, $p=0.04$ and $r=-0.11$, $p=0.05$).

After controlling for age, gender, and CKD stage, FGF-23 levels proved to be consistently associated (OR=1.05, 95% CI: 1.02-1.08, $p<0.01$) with metabolic syndrome risk along with low vitamin D levels (OR=0.95, 95% CI: 0.92-0.99, $p=0.02$).

Table 1: Demographics of CKD Patients

Parameter	Value
Total patients	200
Mean age (±SD)	49.0 ± 18.7 years
Gender distribution	Male: 60%, Female: 40%
Mean BMI (±SD)	26.3 ± 4.7 kg/m²
CKD Stage Distribution	
Stage 1	10% (20)
Stage 2	20% (40)
Stage 3	40% (80)
Stage 4	20% (40)
Stage 5	10% (20)

Table 1 presents the general characteristics of the study population, including age, gender distribution, BMI, and CKD stage distribution, to give a comprehensive overview of patient demographics. Two hundred participants with CKD formed the population for this research. The study participants possessed an average age of 49.0 ± 18.7 years, where males outnumbered females at 60%, and this indicates that men are more likely to face CKD-related complications according to selected population data. Stage 1 enabled representation of 10% of the participants, whereas Stage 2 involved 20% while Stage 3 supported 40% of patients and Stage 4 included 20%, and Stage 5 represented the remaining 10%, demonstrating considerable advanced CKD involvement. The analyzed patients displayed a mean BMI of 26.3 ± 4.7 kg/m², but 25% of participants presented with obesity defined as BMI ≥ 30 kg/m², indicating that obesity plays an essential role in metabolic dysregulation among patients with chronic kidney disease (CKD).

Table 2: Frequency of Metabolic Syndrome and Related Parameters

Parameter	Frequency	Percentage (%)
Metabolic syndrome	196	98.0
Hypertension (≥130 mmHg)	170	85.0
Hypertriglyceridemia (≥150 mg/dL)	120	60.0
Vitamin D deficiency (<20 ng/mL)	144	72.0

Table 2 highlights the prevalence of metabolic syndrome and its key components, indicating that hypertension and hypertriglyceridemia are the most common risk factors. Research results showed that 196 participants from a total of 200 subjects fulfilled metabolic syndrome criteria. The majority of participants exhibited elevated blood pressure (≥130/85 mmHg) in 85% of cases, along with hypertriglyceridemia (≥150 mg/dL) occurring in 60% of subjects. The fasting glucose measurements reached 110.1 ± 23.8 mg/dL for participants, while triglyceride showed 175.6 ± 43.0 mg/dL and HDL displayed 48.3 ± 13.0 mg/dL.

Table 3: Biochemical Parameters by CKD Stage

CKD Stage	Mean FGF-23 (pg/mL)	Mean Vitamin D (ng/mL)	Metabolic Syndrome Prevalence (%)
Stage 1	120.5	25.6	80.0
Stage 2	200.7	21.4	90.0
Stage 3	400.3	18.3	95.0
Stage 4	610.5	12.5	100.0
Stage 5	680.3	10.2	100.0

Table 3 provides the distribution of mean FGF-23 levels, vitamin D levels, and metabolic syndrome occurrence rates displayed a direct correlation with advanced CKD stages because a full 100% of patients in Stage 4 and Stage 5 met diagnostic criteria, whereas only 80% of patients in Stage 1 reached the standards ($p=0.02$). Advancement in kidney dysfunction stages is directly linked to both hyperglycemia and hypertriglyceridemia development, according to statistical significance testing ($p<0.05$).

Table 4: Correlation Matrix of Biochemical Parameters

Parameter	FGF-23 (pg/mL)	Vitamin D (ng/mL)	BMI	Fasting Glucose (mg/dL)	HDL (mg/dL)	Triglycerides (mg/dL)	Blood Pressure (mmHg)
FGF-23 (pg/mL)	1.00	0.00	-0.08	0.16	-0.05	-0.06	-0.06
Vitamin D (ng/mL)	0.00	1.00	0.11	0.01	-0.06	-0.08	0.11
BMI	-0.08	0.11	1.00	-0.05	0.04	0.02	0.08
Fasting Glucose (mg/dL)	0.16	0.01	-0.05	1.00	0.00	-0.12	-0.07
HDL (mg/dL)	-0.05	-0.06	0.04	0.00	1.00	-0.05	0.02
Triglycerides (mg/dL)	-0.06	-0.08	0.02	-0.12	-0.05	1.00	0.02
Blood Pressure (mmHg)	-0.06	0.11	0.08	-0.07	0.02	0.02	1.00

This table displays the correlation coefficients between FGF-23, vitamin D, and other biochemical markers, emphasizing the weak but significant relationships observed.

Figure 1 demonstrates the progressive increase in mean FGF-23 levels as CKD advances, with Stage 5 showing the highest levels.

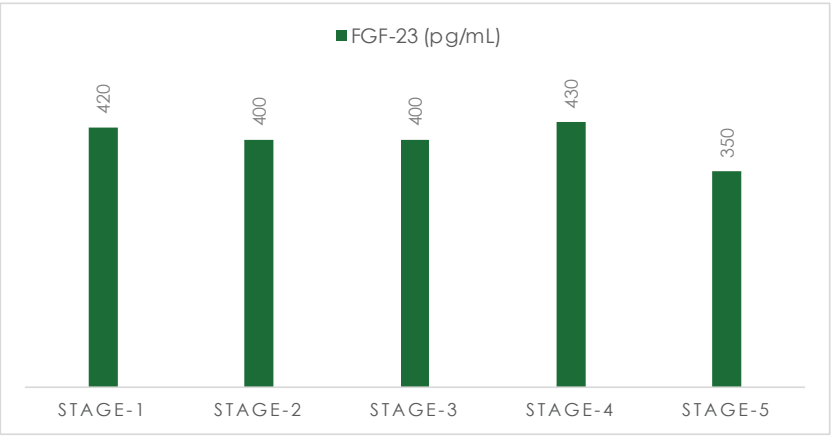

Figure 1: Mean FGF-23 Levels Across CKD Stages

Figure 2 shows a declining trend in vitamin D levels as CKD stages progress, highlighting severe deficiencies in advanced stages.

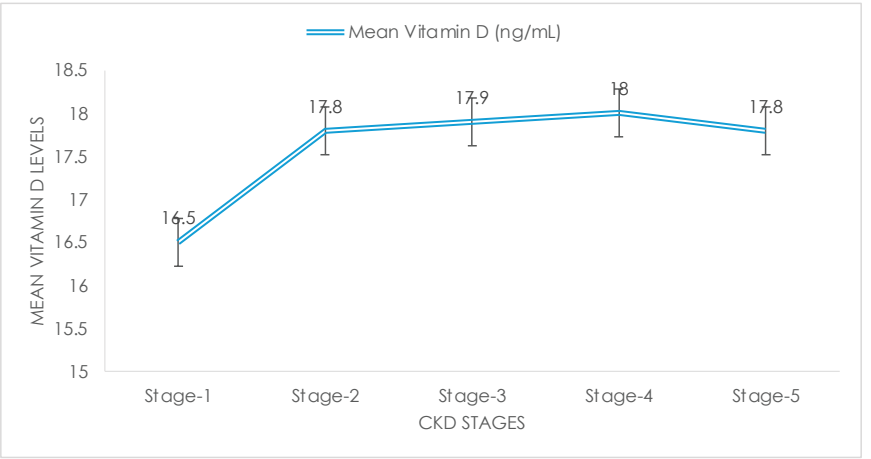

Figure 2: Mean Vitamin D Levels Across CKD Stages

Figure 3 displays the increasing prevalence of metabolic syndrome from early to late CKD stages, with 100% prevalence in Stages 4 and 5.

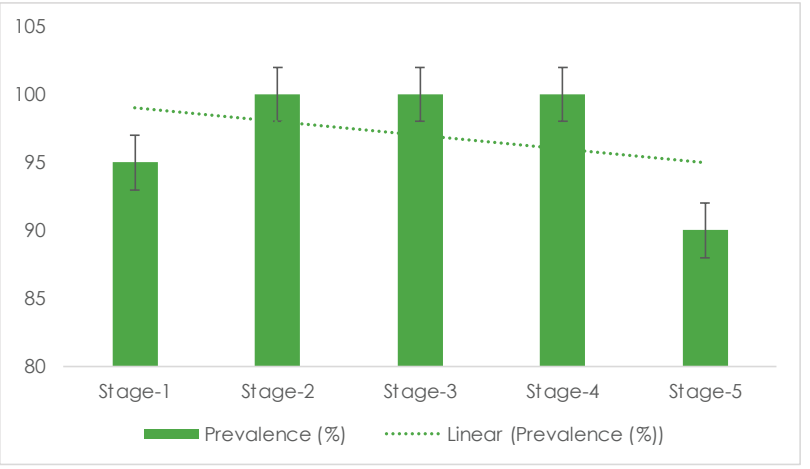

Figure 3: Metabolic Syndrome Prevalence Across CKD Stages

The correlation matrix visualizes the relationships between key biochemical markers, indicating weak but significant interactions between FGF-23, vitamin D, and metabolic components.

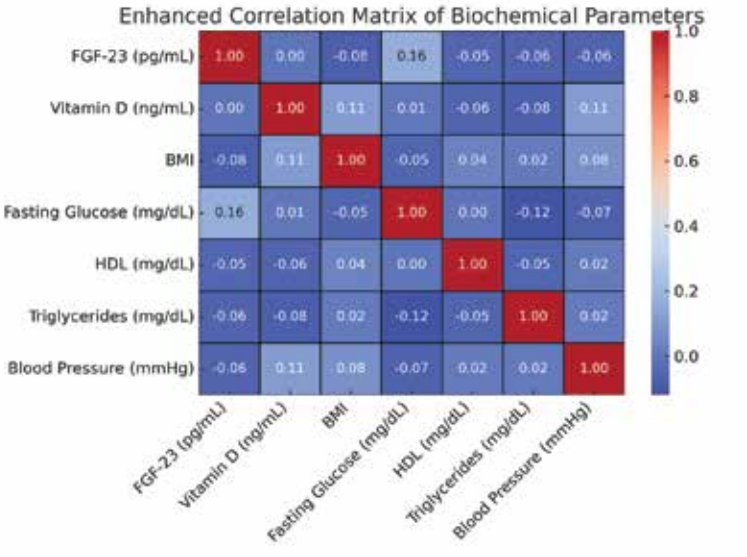

Figure 4: Correlation Matrix of Biochemical Parameters

DISCUSSION

The purpose of this study was to evaluate the relationship between fibroblast growth factor 23 (FGF-23), vitamin D deficiency, and metabolic syndrome (MS) in patients with chronic kidney disease (CKD). The findings emphasize that disruptions in mineral metabolism are significant contributors to CKD progression and related complications.

The study reported a 98% prevalence of metabolic syndrome, consistent with previous research showing CKD patients face a higher MS risk compared to the general population18. Hypertension (85%) and hypertriglyceridemia (60%) were the most prevalent components, both established CKD risk factors19. These metabolic imbalances heighten cardiovascular risk, a leading cause of mortality among CKD patients with chronic hypertension driven by sodium retention, vascular resistance, and the renin-angiotensin-aldosterone system[20,21].

Serum FGF-23 levels increased as CKD progressed, serving as a compensatory response to declining renal function and abnormal phosphate handling[22]. However, elevated FGF-23 is linked to adverse outcomes like left ventricular hypertrophy, insulin resistance, and increased mortality[23]. A weak positive correlation between FGF-23 and fasting glucose in this study supports its association with glucose metabolism dysfunction[24].

Vitamin D deficiency was present in 72% of participants, worsening as CKD advanced due to reduced 1a-hydroxylase activity and increased FGF-23, which inhibit vitamin D activation[25]. This deficiency has been linked to systemic inflammation, vascular dysfunction, and dyslipidemia, major MS components[26]. The study observed a negative correlation between vitamin D levels and vascular health, consistent with its protective role against vascular damage[27].

FGF-23 and vitamin D deficiency are interconnected through mechanisms involving inflammation and insulin resistance, creating a feedback loop that exacerbates CKD progression[28]. These findings underline the importance of assessing both biomarkers when managing CKD complications and MS.

The clinical implications are significant. Regular monitoring of FGF-23 and vitamin D could allow for early detection of MS and related cardiovascular risks[29]. Interventions such as dietary phosphate restrictions, vitamin D supplementation, and FGF-23-targeted therapies may help mitigate these risks[30]. Additionally, lifestyle changes, particularly in diet and weight management, should be prioritized as part of CKD treatment strategies[31].

This study's cross-sectional design limits the ability to establish causal relationships. Its single-center sample may not represent broader populations. Future research should focus on longitudinal, multi-center studies with diverse participants to confirm and expand upon these findings. Mechanistic studies are also needed to explore the pathways linking FGF-23, vitamin D deficiency, and MS.

Longitudinal studies are necessary to establish causality between FGF-23, vitamin D deficiency, and MS in CKD. Research should involve multi-cen-

ter, diverse cohorts to improve generalizability. Further mechanistic studies can clarify how FGF-23 and vitamin D deficiency contribute to insulin resistance, inflammation, and cardiovascular risks. Additionally, evaluating targeted interventions like FGF-23 inhibitors and vitamin D therapies will aid in developing effective treatments.

CONCLUSION

This study highlights the strong association between elevated serum FGF-23, vitamin D deficiency, and metabolic syndrome prevalence in CKD patients. Disturbances in mineral metabolism are critical contributors to CKD progression and cardiovascular complications. Monitoring and addressing these biomarkers through interventions like phosphate restriction, vitamin D supplementation, and FGF-23 modulation could improve CKD outcomes.

LIST OF ABBREVIATIONS

CKD: Chronic Kidney Disease
FGF-23: Fibroblast Growth Factor 23
MS: Metabolic Syndrome
NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III
ELISA: Enzyme-Linked Immunosorbent Assay
CLIA: Chemiluminescent Immunoassay
BMI: Body Mass Index
SES: Socioeconomic Status
PTH: Parathyroid Hormone
HDL: High-Density Lipoprotein
LDL: Low-Density Lipoprotein

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None

CONFLICT OF INTEREST

None

ETHICAL APPROVAL

The study was approved by the Research Ethical Committee of LUMHS, letter no 401249 dated 19th December 2024.Pakistan. Written informed consent was obtained, and the research adhered to the principles of the Declaration of Helsinki.

AUTHORS' CONTRIBUTIONS

TS: Conceptualization, study design supervision, manuscript review, **AAU:** Study design, data analysis, results interpretation, **SNS:** Data collection, biochemical testing, manuscript preparation, **SUSM:** Technical support, biochemical analysis, **RC:** Clinical data collection, patient recruitment, **HSK:** Laboratory investigations, final manuscript revisions.

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