Original Research

Serum Fibroblast Growth Factor 23 and Klotho Levels Correlated With Infection Severity and Pulmonary Function in Patients With Chronic Obstructive Pulmonary Disease Complicated by Pulmonary Infection

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***Running Head*: FGF23/Klotho in COPD With Infection**

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Abstract

Background: Pulmonary infection is a major contributor to clinical deterioration in chronic obstructive pulmonary disease (COPD). The clinical relevance of the FGF23-Klotho axis in infection-related COPD remains unclear.

Methods: A total of 276 COPD patients were enrolled, including 138 with pulmonary infection and 138 matched controls. Serum FGF23 and Klotho were compared across Clinical Pulmonary Infection Score-defined infection severity and COPD phases. Associations with C-reactive protein (CRP), Procalcitonin (PCT), and lung-function parameters were analyzed, and diagnostic performance was assessed by Receiver operating characteristic analysis.

Results: Infected patients showed higher serum FGF23 (91.81 vs. 68.39 pg/mL, $p < 0.001$) and lower Klotho (174.72 vs. 229.38 pg/mL, $p < 0.001$) than controls. FGF23 increased progressively among mild, moderate, and severe infection, whereas Klotho decreased. FGF23 positively correlated with CRP ($r = 0.45$) and PCT ($r = 0.51$), while Klotho showed negative correlations. Both biomarkers were associated with lower Forced expiratory volume in 1 second (FEV_1), FEV_1%pred, and FEV_1/FVC (all $p < 0.001$). The combined FGF23-Klotho model provided the highest diagnostic accuracy (AUC = 0.87).

Conclusion: Pulmonary infection in COPD was characterized by elevated FGF23 and reduced Klotho, closely associated with inflammation, infection severity, and lung-function decline. Combined measurement improved diagnostic accuracy.

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Introduction

Chronic obstructive pulmonary disease (COPD), a heterogeneous and multifactorial disorder, remains a major global cause of morbidity and mortality.[1] COPD involves chronic systemic inflammation and progressive loss of lung function, predisposing patients to acute exacerbations, hospital admissions, and long-term decline.[2] Reductions in FEV_1% predicted have been associated with elevated plasma fibroblast growth factor 23 (FGF23) levels, suggesting that FGF23 may reflect systemic alterations associated with pulmonary function rather than serve as a direct indicator of COPD severity.[2] This substantial global burden highlights the urgent need to elucidate COPD-related pathophysiological mechanisms.

Current assessment of COPD severity relies on spirometry and body plethysmography to quantify FEV_1, Residual Volume/Total Lung Capacity (RV/TLC), and diffusing capacity.[1, 3] Although informative, these measures reflect physiological impairment and lack molecular profiling. Although circulating biomarkers, such as FGF23, have been associated with impaired pulmonary function, their clinical interpretation remains complex because biomarker alterations may reflect multiple processes, including chronic inflammation, tissue remodeling, and systemic responses associated with COPD. Therefore, further validation is required before their incorporation into routine clinical assessment.

FGF23 and its co-receptor Klotho form a signaling axis with emerging relevance in COPD pathobiology.[4] FGF23 functions as a pro-inflammatory hormone capable of activating pathways, such as FGFR/YAP, thereby promoting tissue injury and contributing to accelerated functional decline.[2, 5] Circulating FGF23 levels are markedly elevated in COPD and negatively correlate with pulmonary function metrics, including FEV_1% predicted.[1, 2] In contrast, Klotho, an anti-aging protein with anti-inflammatory and antioxidant effects, supports preservation of lung

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structure and function.[6, 7] Experimental studies suggest that Klotho contributes to pulmonary epithelial protection by regulating oxidative stress, inflammatory responses, and mucociliary function.[4, 6, 7] Clinical studies demonstrated reduced serum Klotho levels in COPD, with lower circulating Klotho concentrations associated with COPD prevalence and disease-related alterations.[8, 9] However, the relationship between circulating Klotho levels and COPD appears to be more complex than a simple deficiency model. A recent population-based study by Yan et al. demonstrated a nonlinear association between serum α-Klotho concentration and COPD risk, showing decreased COPD risk with increasing Klotho levels approximately 1,500 pg/mL but increased risk at higher concentrations, suggesting a potential dose-dependent and context-specific role of Klotho in COPD pathogenesis.[10] Importantly, the temporal variability of circulating Klotho levels has been evaluated in stable COPD patients. Pako et al. reported low day-to-day variability of plasma Klotho concentrations and found that Klotho levels remained unchanged despite improvements in exercise capacity after pulmonary rehabilitation, suggesting that circulating Klotho concentrations may reflect relatively stable biological characteristics rather than short-term changes related to exercise intervention.[11]

Despite these advances, previous studies have mainly focused on stable COPD populations or disease prevalence, while the clinical relevance of the FGF23-Klotho axis during different inflammatory states remains insufficiently characterized. COPD is characterized by persistent airway inflammation and systemic inflammatory alterations, whereas infectious exacerbations represent distinct clinical events associated with acute inflammatory activation. Therefore, circulating biomarker alterations observed in COPD patients may reflect both chronic disease-related processes and infection-associated inflammatory responses, highlighting the importance of distinguishing these inflammatory states when interpreting the clinical significance of the

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FGF23-Klotho axis.[12, 13]

Although previous studies have linked FGF23 elevation and altered Klotho concentrations with COPD development and severity,[1, 2, 8, 9] the biological interpretation of these changes remains uncertain. Specifically, whether the FGF23-Klotho axis reflects lung function impairment, systemic inflammation, or infection-related alterations in COPD remains insufficiently characterized. Consequently, the diagnostic and prognostic value of this axis across different stages of COPD remains insufficiently defined, limiting its translational applicability. Therefore, this study aimed to characterize alterations in serum FGF23 and Klotho levels in COPD patients with and without pulmonary infection, determine their associations with lung function and infection severity, and evaluate whether these biomarkers may serve as indicators reflecting COPD-related inflammatory and infectious conditions.

Materials and Methods

Study Population and Sample Collection

Patients diagnosed with COPD were identified through the electronic medical record system of Jiangnan University Medical Center. A consecutive enrollment strategy was applied, and eligible patients were screened according to predefined inclusion and exclusion criteria. A total of 138 COPD patients with pulmonary infection were included. COPD patients without pulmonary infection who met the same eligibility criteria were selected as controls and matched using propensity score matching.

Collected clinical data included demographic characteristics, GOLD classification, CPIS score, CRP and PCT levels, and pulmonary function test results. The study was approved by the Ethics Committee of Jiangnan University Medical Center (#2025-24-5), and written informed consent

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was waived.

Blood samples were collected within 24 h of admission for the infection group, and at the stable-phase outpatient visit for controls. Serum was separated within 2 h and stored at −80 °C until assay and were limited to no more than three freeze-thaw cycles. Only samples with a minimum volume of 0.5 mL and without hemolysis, lipemia, or other contamination were included.

Laboratory Measurements

Serum FGF23 and soluble α-Klotho were quantified by commercial enzyme-linked immunosorbent assay (ELISA) kits following the manufacturers' protocols. FGF23 and soluble α-Klotho was measured with the corresponding ELISA kits (Thermo Fisher). Samples were measured at least in triplicate, concentrations were derived from a four-parameter logistic standard curve, and optical densities were read at 450 nm on a microplate absorbance reader. Values below the detection limit were assigned the lower limit, and values above the upper limit were diluted and re-assayed.

Study Groups and Definitions

A total of 276 COPD patients were enrolled and divided into two groups: COPD with pulmonary infection (n = 138) and COPD without pulmonary infection (n = 138). Patients were enrolled if they met COPD diagnostic criteria (post-bronchodilator $FEV_1/FVC < 0.70$). Pulmonary infection was defined by a CPIS ≥ 4 in conjunction with a positive sputum culture. The infection group was stratified by CPIS severity into mild (n = 48), moderate (n = 64), and severe (n = 26) categories, and by clinical phase into acute exacerbation (n = 97) and stable disease (n = 41). Control patients had a confirmed diagnosis of COPD but no evidence of pulmonary infection, defined as CPIS < 4 and absence of infectious symptoms within the previous three months.

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To minimize confounding and achieve baseline comparability, the infection and control groups were matched in a 1:1 ratio using propensity score matching. Matching variables included sex, age, GOLD classification, and COPD disease phase.

Inclusion criteria

Patients were eligible if they met diagnostic criteria for COPD, defined as a post-bronchodilator $FEV_1/FVC < 0.70$ and an FEV_1% predicted corresponding to GOLD stages 1-4. For the infection group, patients were additionally required to meet established criteria for pulmonary infection, including: (i) a CPIS score ≥ 4; (ii) clinical features indicative of infection, such as fever, increased cough or sputum, or purulent sputum; (iii) newly developed pulmonary infiltrates on imaging; and (iv) identification of pathogenic organisms on sputum culture. We included only individuals who had complete clinical data and serum samples of good quality. Samples had to be free of hemolysis, lipemia, and contamination, and could not undergo more than three freeze–thaw cycles.

Exclusion Criteria

Patients were excluded if they met any of the following conditions: (1) presence of other pulmonary diseases, including bronchial asthma, pulmonary tuberculosis, or lung cancer; (2) severe systemic comorbidities, including severe cardiac dysfunction (NYHA functional class III-IV heart failure or left ventricular ejection fraction <40%), severe hepatic dysfunction (decompensated cirrhosis or severe chronic liver disease with impaired coagulation function), severe renal dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m^2 or requiring renal replacement therapy), active malignancies, or systemic autoimmune diseases requiring immunosuppressive therapy, which could substantially influence inflammatory status, FGF23/Klotho metabolism, or pulmonary function assessment; (3) use of immunosuppressive

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agents or systemic corticosteroids within the preceding month; or (4) serum sample contamination or missing essential clinical data.

COPD Severity Classification and Clinical Staging

The severity of airflow limitation was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[14] Post-bronchodilator FEV_1% predicted was used to define four stages of disease severity: GOLD 1 (mild), FEV_1% predicted ≥ 80%; GOLD 2 (moderate), 50–79%; GOLD 3 (severe), 30–49%; and GOLD 4 (very severe), < 30%.

Clinical status was classified into two categories. The stable phase was defined as chronic respiratory symptoms without acute worsening and no exacerbation in the previous three months. Acute exacerbation was defined as a rapid (<72 hours) increase in respiratory symptoms—such as cough, sputum volume or purulence, or dyspnea—together with a measurable decline in lung function from baseline.

CPIS Assessment

The severity of pulmonary infection was evaluated using the CPIS, a validated composite scoring system integrating six clinical parameters (range 0-12 points), with higher scores indicating more severe infection. The components included: (1) body temperature: 36.5-38.4 °C (0 points), 38.5-38.9 °C or 36.0-36.4 °C (1 point), ≥39.0 °C or ≤35.9 °C (2 points); (2) peripheral white blood cell count: 4.0-11.0 × 10^9/L (0 points), 11.1-17.0 × 10^9/L or 3.0-3.9 × 10^9/L (1 point), >17.0 × 10^9/L or <3.0 × 10^9/L (2 points); (3) tracheal secretions: non-purulent (0 points) or purulent (1 point); (4) chest radiography: no new infiltrates (0 points) or new/progressive infiltrates (2 points); (5) oxygenation (PaO_2/FiO_2): >240 mmHg or presence of ARDS (0 points) versus ≤240 mmHg without ARDS (2 points); and (6) microbiological culture: no pathogen identified (0 points) or growth of a pathogen consistent with the infection site (1 point). Based on the total

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score, infection severity was categorized as mild (CPIS < 6), moderate (CPIS 6-9), or severe (CPIS > 9) for subsequent stratified analyses.

Statistical analysis

Statistical analyses were conducted using SPSS 26.0 and GraphPad Prism 9.0. Normality of distribution for continuous variables was tested using the Shapiro-Wilk test. Normally distributed variables are expressed as mean ± standard deviation (SD), and skewed variables are presented as median (interquartile range, IQR). For between-group comparisons, the Welch-corrected unpaired t test was applied for normally distributed data, and the Mann-Whitney U test was used for skewed data. For multi-group comparisons, one-way analysis of variance (ANOVA) was used for normally distributed data, and the Kruskal-Wallis H test was applied for skewed data. . Categorical variables were analyzed with the χ^2 test or Fisher's exact test. Correlations between serum FGF23, Klotho, inflammatory markers (CRP, PCT), and lung-function parameters (FEV_1, FEV_1%pred, FEV_1/FVC) were assessed using Pearson or Spearman correlation coefficients. Diagnostic performance was evaluated using Receiver operating characteristic (ROC) curve analysis, with AUC, 95% CI, sensitivity, specificity. Baseline comparability between infection and non-infection groups was ensured by 1:1 propensity score matching. A two-sided $P < 0.05$ was considered statistically significant.

Results

Comparisons of baseline clinical data between Two groups

To determine whether subsequent differences between groups could be attributed to pulmonary infection rather than confounding factors, we first compared baseline characteristics between the infection and non-infection COPD groups. As shown in Table 1, age, sex, BMI, COPD duration,

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GOLD stage, clinical phase, and major comorbidities did not differ significantly between groups (all $P > 0.05$), indicating well-matched baseline profiles. In contrast, inflammatory markers were markedly elevated in the infection group, with significantly higher CRP and PCT levels (both $P < 0.001$). Lung-function indices also differed significantly: patients with infection exhibited lower FEV_1, FEV_1% predicted, and FEV_1/FVC (all $P < 0.001$), indicating that pulmonary infection imposed additional airflow limitation and further impaired respiratory function.

Comparisons of serum FGF23 and Klotho levels between infection group and non-infection group

To examine whether pulmonary infection affects mineral-metabolism–related biomarkers in COPD, we compared serum FGF23 and Klotho levels between infected and non-infected patients in both disease phases. In the overall cohort, FGF23 levels were significantly higher in the infection group than in controls (91.81 pg/mL [IQR 74.11–111.20] vs. 68.39 pg/mL [IQR 55.38–80.42], $p < 0.001$; Figure 1A), a pattern that remained evident in both the stable phase (94.27 pg/mL [IQR 66.68–109.70] vs. 71.53 pg/mL [IQR 56.17–85.57]; Figure 1B) and acute exacerbations (91.47 pg/mL [IQR 74.48–111.29] vs. 66.51 pg/mL [IQR 54.86–78.48], $p < 0.001$; Figure 1C). Conversely, Klotho concentrations were markedly lower in infected patients (174.72 pg/mL [IQR 124.43–205.55] vs. 229.38 pg/mL [IQR 179.92–272.86]; Figure 1D), with consistent reductions in the stable phase (184.57 pg/mL [IQR 147.03–203.92] vs. 233.71 pg/mL [IQR 197.54–274.48]; Figure 1E) and a more significant decline during exacerbations (162.60 pg/mL [IQR 118.41–208.93] vs. 222.39 pg/mL [IQR 174.23–269.45]; Figure 1F). Together, these findings indicated that pulmonary infection in COPD was characterized by elevated FGF23 and suppressed Klotho, with greater deviations during acute exacerbations, suggesting their relevance as biomarkers of infection-related metabolic and inflammatory dysregulation.

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Diagnostic Performance of Serum FGF23 and Klotho

To assess the diagnostic utility of FGF23 and Klotho for identifying pulmonary infection in COPD, we performed ROC analyses for each biomarker alone and in combination. FGF23 exhibited moderate diagnostic discrimination, yielding an AUC of 0.75 (95% CI, 0.69–0.81), an optimal cutoff value of 83.74 pg/mL, and corresponding sensitivity and specificity values of 74.57% and 72.54%, respectively (Figure 2, Table 2). Klotho showed comparable performance (AUC 0.73; 95% CI, 0.67–0.79) with a cutoff of 205.0 pg/mL, yielding 75.36% sensitivity and 63.04% specificity. The combined model (0.037 × FGF23 – 0.013 × Klotho) markedly improved diagnostic accuracy, achieving an AUC of 0.87 (95% CI, 0.83–0.91), along with higher sensitivity (86.96%), specificity (75.46%), and the greatest Youden index (0.62). These findings indicated that while each biomarker alone provided moderate diagnostic value, their combined assessment substantially enhanced discrimination of pulmonary infection in COPD.

Associations of FGF23 and Klotho with Infection Severity

To clarify how infection severity influences mineral-metabolism–related biomarkers in COPD, we compared serum FGF23 and Klotho across mild, moderate, and severe infection subgroups and examined their relationships with systemic inflammation. FGF23 showed a clear severity-dependent rise, increasing from 82.95 pg/mL (IQR 61.02–96.53) in mild infection to 91.59 pg/mL (IQR 80.07–111.43) in moderate infection and 109.7 pg/mL (IQR 97.25–121.17) in severe infection (Figure 3A; all pairwise $p < 0.05$). In contrast, Klotho declined stepwise with increasing severity, with median levels of 187.33 pg/mL (IQR 152.43–232.03), 172.04 pg/mL (IQR 123.46–201.67), and 121.22 pg/mL (IQR 94.38–185.41) across the three subgroups (Figure 3D; all $P < 0.05$). Correlation analysis supported these patterns: FGF23 was positively correlated with CRP ($r = 0.45$) and PCT ($r = 0.51$), whereas Klotho showed negative correlations with CRP

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(r = –0.43) and PCT (r = –0.48) (Figure 3B, C, E, F). Taken together, these findings showed that more severe infections were associated with higher FGF23 and lower Klotho levels, both of which were closely associated with systemic inflammation.

FGF23 Elevation and Klotho Suppression Correlate with Lung Function Decline

To assess how mineral-metabolism–related biomarkers relate to lung function in COPD complicated by pulmonary infection, we analyzed correlations between serum FGF23, Klotho, and core spirometric indices. FGF23 demonstrated consistent inverse associations with lung function, negatively correlating with FEV_1 (r = -0.42), FEV_1%pred (r = -0.36), and FEV_1/FVC (r = -0.41) (Figure 4A-C). In contrast, Klotho showed positive correlations with FEV_1 (r = 0.38), FEV_1%pred (r = 0.40), and FEV_1/FVC (r = 0.44) (Figure 4D-F). These relationships indicated that higher FGF23 and lower Klotho levels were closely associated with more severe airflow limitation, underscoring a strong association between FGF23-Klotho axis dysregulation and impaired pulmonary function in infection-related COPD.

Discussion

In this study, we identified a consistent pattern of dysregulated mineral-metabolism biomarkers in COPD patients with pulmonary infection, marked by increased circulating FGF23 and reduced Klotho levels. These changes were evident across clinical phases, showed clear severity-related gradients, and were associated with greater systemic inflammation and worse lung function. Taken together, these findings suggest that disruption of the FGF23-Klotho axis may be associated with infection-related inflammatory burden and airflow limitation in COPD. Mechanistically, the infection-related rise in FGF23 may involve multiple inflammatory and metabolic pathways. Acute infection rapidly induces IL-6, TNF-α, and IL-1β, which directly

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stimulate FGF23 transcription and processing in osteocytes and renal tissues,[15] superimposed on the chronically elevated cytokine milieu characteristic of COPD.[12] Infection-driven airway inflammation also activates the lung–bone marrow axis, mobilizing hematopoietic and inflammatory cells that intensify distal-organ inflammatory signaling and promote FGF23 synthesis.[16, 17] Concurrent oxidative stress, infection-induced functional iron deficiency, and HIF-1α activation further augment FGF23 production through iron-regulatory and hypoxia-responsive pathways.[13, 15, 18]

In parallel, infection further suppresses Klotho expression, which is already reduced in COPD,[4] thereby removing a critical inhibitory component of the FGF23–Klotho complex. Loss of Klotho permits aberrant FGFR4 activation,[4] promoting downstream NF-κB–dependent cytokine release.[19, 20] These inflammatory, metabolic, and receptor-level pathways may provide a potential biological explanation for the observed association between elevated FGF23 and infection severity in COPD. However, whether FGF23 directly contributes to inflammatory amplification during infection requires further experimental validation. This integrated mechanism may provide a plausible explanation for the graded increase in FGF23 observed across infection-severity strata in COPD.

The direction of the Klotho change during inflammation merits explicit consideration. In principle, an antioxidant defense system might be expected to rise as a compensatory response to inflammatory stress, and modest increases in soluble α-Klotho have indeed been reported in some chronic inflammatory states. In COPD, however, the dominant evidence points to active suppression rather than compensatory elevation. Pro-inflammatory cytokines, particularly TNF-α and TWEAK, downregulate Klotho expression through NF-κB-dependent binding of RelA to the Klotho promoter and associated histone deacetylation. In airway epithelial cells, cigarette smoke

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extract combined with TNF-α almost completely suppresses Klotho release. Klotho expression is already reduced in COPD lungs and falls further with inflammatory exposure. Thus, the lower Klotho levels observed in infected patients are unlikely to reflect a simple "emptying" of a circulating reservoir; they more plausibly reflect inflammation-driven transcriptional silencing superimposed on the chronically reduced Klotho expression characteristic of COPD itself.

In COPD complicated by infection, the elevation of FGF23 appears to arise from the coordinated action of inflammatory pathways, particularly those that enhance its transcription and secretion. Previous studies demonstrate that FGF23 associates closely with inflammatory markers; notably, intact FGF23 correlates strongly with IL-6 and TNF-α, suggesting that these cytokines may drive FGF23 production through stimulation of osteocytes or other responsive cell types.[21] Both in vitro and in vivo models further show that exposure to cigarette smoke or FGF23 activates FGFR4 in a Klotho-independent manner, triggering the PLCγ/NFAT pathway and markedly increasing IL-1β release.[4] This mechanism is likely amplified during acute infection, forming a positive feedback loop in which infection-induced systemic inflammation (e.g., rising IL-6 and TNF-α) enhances FGF23 synthesis, and elevated FGF23 has been proposed to interact with inflammatory signaling pathways and may contribute to the inflammatory alterations observed in COPD patients with infection[4]. Neutrophil activation and potential bone-marrow–derived feedback responses may contribute additional regulatory layers.[2]

In parallel, circulating Klotho is markedly reduced in infection-related COPD, a phenomenon attributable to chronic inflammatory stress that suppresses Klotho expression. Klotho downregulation has been documented in airway epithelial cells and alveolar macrophages, particularly under cigarette-smoke exposure, supporting the notion that Klotho silencing is a key component of COPD-associated inflammation.[9, 22] However, reduced circulating Klotho levels

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are not specific to COPD. Decreased Klotho concentrations have also been reported in other chronic inflammatory conditions, including autoimmune diseases,[23] obstructive sleep apnea,[24] and periodontitis,[25] suggesting that Klotho reduction may represent a broader biological response associated with chronic inflammation, oxidative stress, and aging-related processes rather than a disease-specific alteration. Given Klotho's intrinsic anti-inflammatory and antioxidative properties, its reduction may contribute to impaired regulation of inflammatory responses and increased susceptibility to tissue injury in COPD. In Klotho-deficient mouse models, loss of Klotho recapitulates COPD-like pathology, including airway inflammation and emphysematous changes.[26] Although direct correlations between Klotho and specific cytokines are not uniformly quantified across datasets, experimental evidence consistently supports a negative association between Klotho and inflammatory burden.[27] The progressive fall in Klotho with increasing infection severity suggests exhaustion of a critical anti-inflammatory defense mechanism, potentially exacerbating tissue injury.[10]

Disruption of the FGF23–Klotho signaling axis may represent an important component associated with infection-related inflammatory alterations in COPD. The reciprocal pattern of rising FGF23 and falling Klotho underscores the axis-level dysregulation that becomes particularly pronounced during infection.[4] Integrated biomarker analyses further show that FGF23 correlates negatively with lung-function indices, including FEV_1 and FEV_1% predicted, indicating its close relationship with declining ventilatory capacity.[1] Conversely, Klotho is inversely associated with COPD risk and implicitly linked to preserved lung function,[8] consistent with its protective biological role. Dysregulation of this axis not only amplifies inflammatory pathways (e.g., NFAT-dependent cytokine production) but also directly affects airway structure and mechanics, thereby promoting airflow limitation and loss of pulmonary function.[1] Together,

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these findings position the disturbed FGF23-Klotho axis as a mechanistic framework for understanding the integrated metabolic–inflammatory biology of COPD during infection, in which infection-associated alterations in the FGF23-Klotho axis may be involved in inflammatory dysregulation and impaired pulmonary function.

From a translational perspective, our diagnostic analyses reveal that while FGF23 and Klotho individually exhibit moderate discriminative ability for identifying pulmonary infection, their combined assessment substantially enhances diagnostic accuracy. The dual-marker model achieved an AUC of 0.87 and the highest Youden index, outperforming either biomarker alone. These findings indicate that the FGF23-Klotho axis may serve as a complementary biomarker panel for identifying COPD patients with infection-related inflammatory alterations. Although these findings provide a basis for further clinical investigation, prospective longitudinal studies are required to determine whether incorporating these biomarkers into existing clinical assessment models can improve prediction accuracy and support individualized patient evaluation.

Several limitations should be noted. First, this was a single-center study, which may limit the generalizability of the findings. Second, the cross-sectional design precludes causal inference regarding whether dysregulation of the FGF23-Klotho axis contributes to infection susceptibility or progression. Third, mechanistic pathways were not directly interrogated; future studies using cellular and animal models with targeted modulation of FGF23-Klotho signaling are needed to determine whether this axis directly regulates inflammatory responses during COPD exacerbation and to clarify downstream molecular mechanisms.

Conclusion

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In conclusion, pulmonary infection in COPD is associated with a distinct disruption of the FGF23–Klotho axis that corresponds to inflammatory burden, infection severity, and the degree of airflow limitation. Combined measurement of FGF23 and Klotho provides better diagnostic discrimination than either marker alone, indicating their potential value as complementary biomarkers for identifying infection-associated inflammatory alterations in COPD. Prospective longitudinal studies with serial measurements of FGF23 and Klotho during COPD exacerbation and recovery, together with mechanistic studies using cellular and animal models, are warranted to determine the temporal relationship and causal role of the FGF23-Klotho axis in infection-related COPD.

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Declaration of competing interest

The authors declare that there is no conflict of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Author contributions

Ruiqi Luo and Suping Tang conducted the experiments, analyzed the data, and wrote the manuscript. Suping Tang conceived and supervised the study.

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Table 1. Comparisons of baseline clinical data between the infection group and non-infection group in patients with COPD.

Factors	Infection (n=138)	Non-infection (n=138)	P value
Age (years)	58.67 ± 7.42	59.31 ± 8.11	0.492
BMI (kg/m^2)	22.45 ± 1.53	22.71 ± 1.48	0.329
Gender, n (%)			
Male	86 (62.3)	80 (57.9)	0.539
Female	52 (37.7)	58 (42.1)	
COPD Duration, n (%)			
< 5 years	54 (39.1)	59 (42.8)	0.625
≥ 5 years	84 (60.9)	79 (57.2)	
GOLD Stage, n (%)			
GOLD Stage 1-2	50 (36.2)	56 (40.6)	0.536
GOLD Stage 3-4	88 (63.8)	82 (59.4)	
COPD Phase, n (%)			
Stable Phase	41 (29.7)	52 (33.3)	0.203
Acute Exacerbation Phase	97 (70.3)	86 (66.7)	
Hypertension			
Yes	46 (33.3)	41 (29.7)	0.604
No	92 (66.7)	97 (70.3)	
Diabetes Mellitus			
Yes	28 (20.3)	25 (18.1)	0.760
No	110 (79.7)	113 (81.9)	
CRP (mg/L)	24.87 (17.40 ~ 32.88)	8.43 (6.14 ~ 11.57)	< 0.001
PCT (ng/mL)	2.05 (1.16 ~ 3.28)	0.38 (0.27 ~ 0.53)	< 0.001
FEV1 (L)	1.47 ± 0.46	1.73 ± 0.52	< 0.001
FEV_1%pred	42.73 ± 6.92	48.76 ± 7.13	< 0.001
FEV1/FVC (%)	52.44 ± 4.77	57.32 ± 5.16	< 0.001

Data are presented as n (%) for categorical variables. For continuous variables, normally distributed data (age, BMI, FEV_1, FEV_1%pred, FEV_1/FVC) are expressed as mean ± SD, while skewed data (CRP, PCT) are presented as median (IQR). Fisher's exact test was used for categorical variables. The Welch-corrected unpaired t test and Mann-Whitney U test were applied for normally and skewed continuous variables, respectively.

BMI: Body mass index, GOLD: Global Initiative for Chronic Obstructive Lung Disease, CRP: C-reactive protein, PCT: Procalcitonin, FEV1: Forced expiratory volume in 1 second, FEV1/FVC: Ratio of forced expiratory volume in 1 second to forced vital capacity, FEV_1%pred: Forced expiratory volume in 1 second as a percentage of predicted value.

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Table 2. Diagnostic values in ROC analysis.

	Cut off	AUC	95% CI	p	Sensitivity (%)	Specificity (%)	Youden index
Serum FGF23	83.74 pg/mL	0.75	0.69 to 0.81	<0.001	74.57	72.54	0.47
Serum Klotho	205.0 pg/mL	0.73	0.67 to 0.79	<0.001	75.36	63.04	0.38
FGF23+Klotho	-	0.87	0.83 to 0.91	<0.001	86.96	75.46	0.62

CI: confidence interval.

COMPUTE FGF23+Klotho = 0.037 * FGF23 - 0.013 * Klotho.

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Figure legends

Figure 1. Comparisons of serum FGF23 and Klotho levels between infection group and non-infection group stratified by COPD phase. Serum FGF23 levels in total population (A), stable phase (B), and acute exacerbation phase (C). D-F: Serum Klotho levels in total population (D), stable phase (E), and acute exacerbation phase (F). Violin plots visualize the probability density of data distribution. Inner box plots indicate the median and interquartile range (IQR), and whiskers extend to the minimum and maximum observed values. Statistical comparisons were performed using the Mann-Whitney U test. $p < 0.001$ indicates a statistically significant difference between groups.

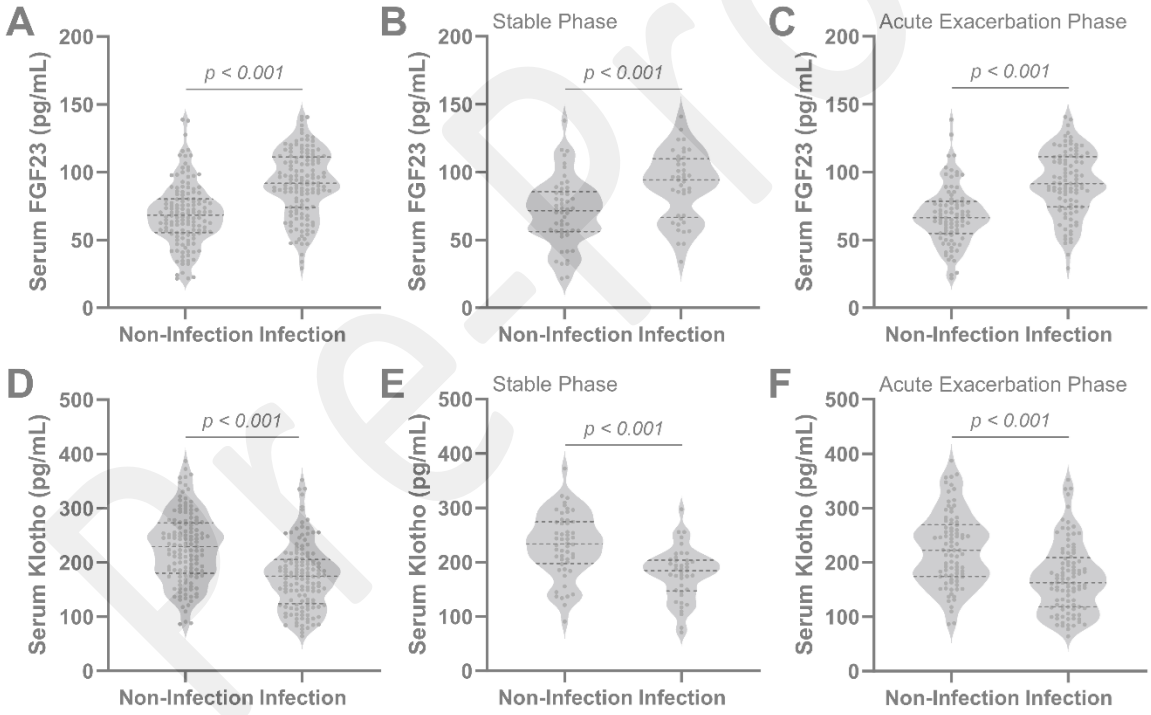

Figure 2. ROC curves of serum FGF23, Klotho alone and in combination for diagnosing COPD complicated by pulmonary infection.

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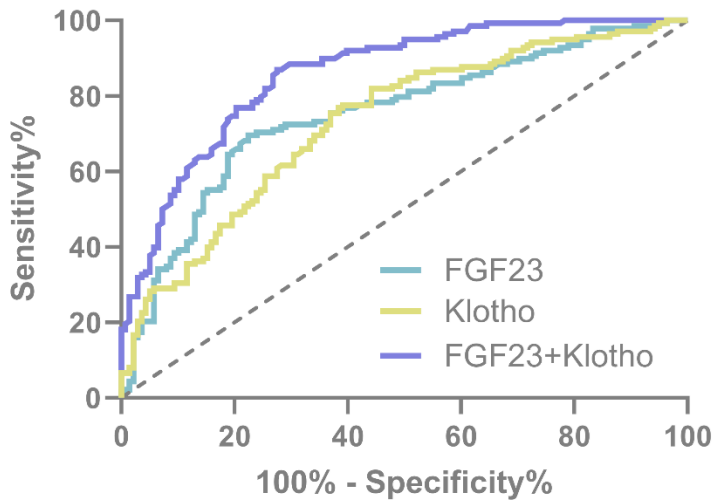

Figure 3. Correlation analysis between serum FGF23, Klotho levels with severity of infection. (A) Serum FGF23 levels in mild, moderate, and severe infection subgroups. Correlation between FGF23 with CRP (B) and PCT (C) in COPD patients complicated by pulmonary infection. (D) Serum Klotho levels in mild, moderate, and severe infection subgroups. Correlation between Klotho with CRP (E) and PCT (F) in COPD patients complicated by pulmonary infection. Data in A and D are presented as violin plots with inner box plots indicating the median and interquartile range (IQR) and whiskers extending to the minimum and maximum observed values. Statistical analysis was performed using Kruskal-Wallis H test. Correlation analysis was performed by Spearman correlation coefficient.

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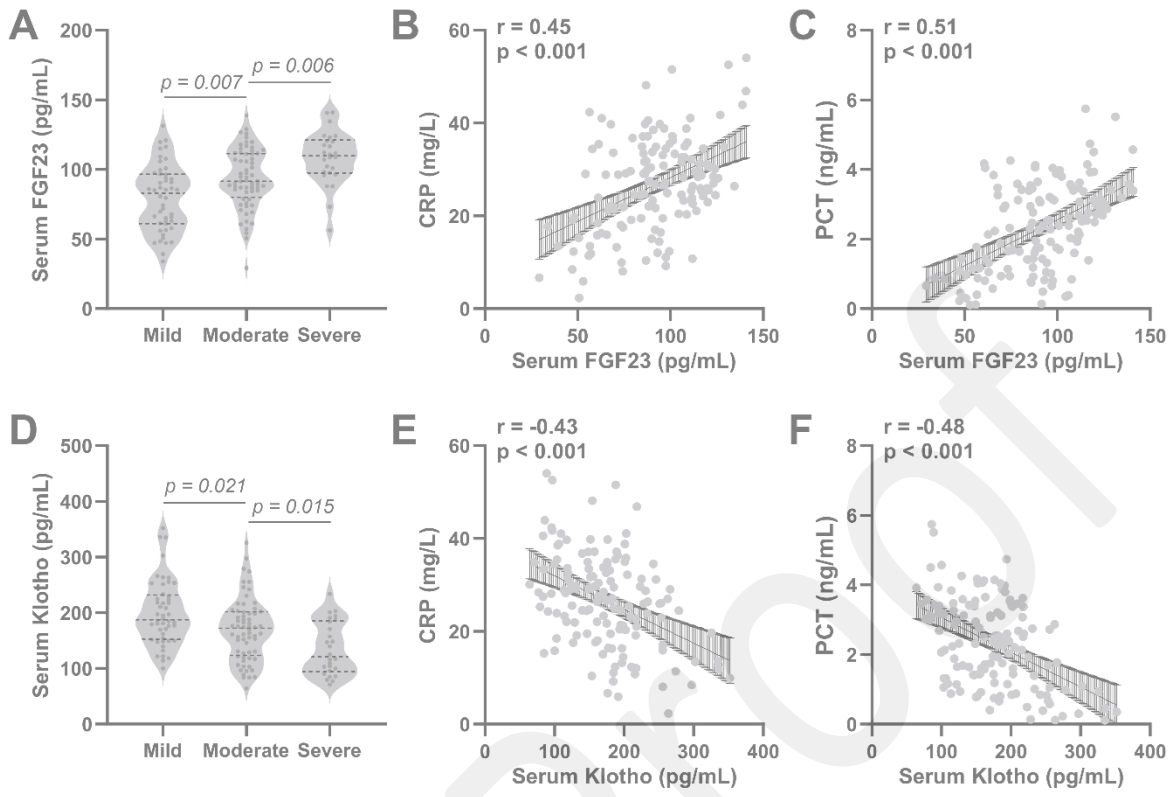

Figure 4. Correlation between FGF23 with FEV1 (A), FEV1%pred (B), and FEV1/FVC (C) in COPD patients complicated by pulmonary infection. Correlation between Klotho with FEV1 (D), FEV1%pred (E), and FEV1/FVC (F) in COPD patients complicated by pulmonary infection. Correlation analysis was performed by Spearman correlation coefficient.

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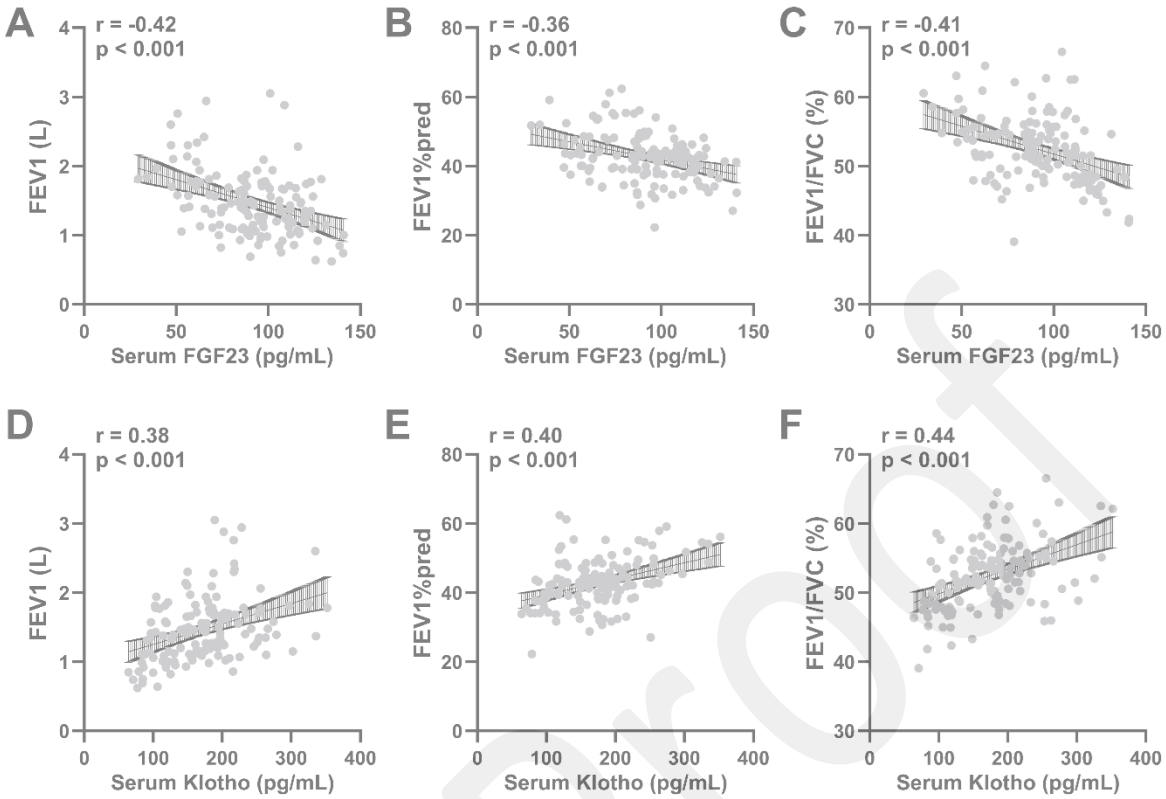

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