Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2025 [Online ahead of print]

To cite this Article:
Singh S, Jaggi S, Gupta S, et al. **Evaluation of fibroblast growth factor 23 as a marker of severity in stable chronic obstructive pulmonary disease.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2025.3271

Evaluation of fibroblast growth factor 23 as a marker of severity in stable chronic obstructive pulmonary disease

Simarpreet Singh,[1] Surabhi Jaggi,[2] Seema Gupta,[3] Deepak Aggarwal,[1]
Mandeep Kaur Sodhi,[1] Chahat Bhatia,[1] Varinder Saini[1]

[1]Department of Pulmonary, Critical Care and Sleep Medicine, Government Medical College and Hospital, Chandigarh; [2]Department of Pulmonary Medicine, Indira Gandhi Medical College, Shimla, Himachal Pradesh; [3]Department of Biochemistry, Government Medical College and Hospital, Chandigarh, India

Correspondence: Surabhi Jaggi, Department of Pulmonary Medicine, Second floor, D Block, Indira Gandhi Medical College, Shimla 171001, India.
Tel.: +918968634206. E-mail: surabhijaggi@gmail.com

Contributions: SS, SJ, SG, DA, MKS, CB, VS helped in the treatment of the patients, helped in retrieving the data and conceived the content of the manuscript. SS and CB drafted the manuscript. All authors read and revised the manuscript critically for important intellectual concepts and SG, VS, SJ, DA and MKS approved the final version of the manuscript.

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: the study protocol was reviewed and approved by the Institutional Ethics Committee, GMCH (Government Medical College and Hospital, Sector 32, Chandigarh, India) with document approval number GMCH/IEC/774R/2022/189.

Informed consent: witten informed consent for the use of data was obtained from the index cases during the study.

Patient consent for publication: obtained.

Availability of data and materials: data and materials are available from the corresponding author upon request.

Funding: none.

Abstract

Chronic obstructive pulmonary disease (COPD), a multi-component disease, is one of the leading causes of morbidity and mortality globally. Considering the drawbacks of current severity markers of COPD, there is a need to find newer alternatives that are easily accessible and provide insight into the underlying pathophysiology of the disease. This study evaluated fibroblast growth factor 23 (FGF23), a pro-inflammatory hormone, as a severity marker for COPD. A total of 54 stable COPD patients were recruited as per the inclusion and exclusion criteria. All participants were subjected to spirometry and body plethysmography with diffusion capacity of lungs for carbon monoxide (DLCO) evaluation. Plasma FGF23 levels were measured for all participants. This study aimed to evaluate FGF23 as a severity indicator of COPD, along with its association with serum phosphate levels, static lung volumes, and DLCO. The mean age of the study population (n=54) was 59±11 years. The majority of study participants had moderate COPD (50%), followed by severe (27.8%), mild (20.4%), and very severe (1.9%). The mean plasma FGF23 value observed was 115±169 pg/mL. A significant negative correlation was observed between FGF23 levels and forced expiratory volume in 1 second (FEV1) (% predicted), demonstrating the diagnostic role of FGF23. The phosphaturic action of FGF23 was validated by a strong negative correlation observed between serum phosphate and plasma FGF23 levels. Receiver-operating characteristic curve analysis of FGF23 showed that cut-off levels of 73.71 pg/mL can be used to distinguish mild to moderate COPD from severe to very severe, with a sensitivity and specificity of 62.5% and 68.4%, respectively. FGF23 levels were found to be significantly increased in individuals with poor lung function and compromised lung volumes. FGF23 levels were negatively correlated with FEV1 (% predicted) and can be used as a potential severity marker. Hence, plasma FGF23 levels showed a promising role as a severity marker of COPD.

Key words: COPD, FGF23, spirometry, DLCO.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) refers to a variety of lung conditions that are characterized by persistent, frequently progressive airflow obstruction caused by abnormalities of the airways and/or alveoli [1]. COPD is one of the leading causes of morbidity and mortality globally, with highest burden in low and middle-income countries [2].

COPD is suspected in patients with pertinent clinical symptoms who are subjected to spirometry, in which presence of a post-bronchodilator forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC) ratio less than 0.70 confirms the presence of persistent airflow limitation [3]. FEV1 is currently the most commonly used indicator of disease severity and progression of COPD. However, is not always able to reveal the whole complexity of the illness [4]. It poorly correlates with clinical presentation of patient and its symptoms. Also, it cannot differentiate among different causes of airflow limitation and does not help in identifying extra pulmonary manifestations of COPD. The decision whether to use FEV1/FVC ratio or the lower limit of normal (LLN), and pre- or post-bronchodilator spirometry, is challenging. While one parameter might diagnose a patient as COPD, other might not [5]. The existing discrepancy among different parameters and lack of evidence of standardization makes interpretation and diagnosis difficult.

High resolution computed tomography (HRCT) chest can identify the degree of emphysema but it provides less information in cases of patients of chronic bronchitis. It does not correlate with clinical severity of the disease. Some patients may exhibit severe emphysema on HRCT chest while spirometry may grade the disease to be mild and vice-versa.

In order to fill the existing gap in diagnosis of COPD, many biomarkers have been identified. Initial studies and research papers consistently observed hypophosphatemia in patients of COPD. Serum phosphate levels were correlated with degree of respiratory muscle failure and increased morbidity. This further emphasized the need to explore and find cause for hypophosphatemia in COPD and its role in pathophysiology of the disease. This brought Fibroblast Growth Factor 23 (FGF23) into the picture.

The hormone FGF23, which is produced from bones and controls phosphate metabolism, is synthesised in response to blood phosphate levels [6]. It is widely known that FGF23 serves as a phosphaturic hormone in context of chronic renal disease. This circulating pro-inflammatory hormone plays a notable part in augmenting COPD related inflammation via alpha-klotho, its co-receptor. A detrimental cycle of frequent hospitalization, increased cardiovascular risk, acute

worsening and mortality has been observed in frequent exacerbators of COPD, attributing to persistent systemic and airway inflammation [7].

Current evidence suggests either a direct or an indirect role of FGF23 in the complex pathophysiology of COPD, hence augmenting a need to explore the area and establish a link between the two. However, data on its role as a severity marker is scarce both from India and outside. Considering the drawbacks of currently available markers, there is an urge to identify newer modalities. If association between FGF23 levels and COPD is established, it would serve as an important severity marker and help optimizing treatment. Hence, the current study correlated serum FGF23 levels with existing indicators of severity and lung functions, and evaluated its validity to serve as a severity marker for COPD.

Materials and Methods

The study is a cross-sectional study conducted in the Department of Pulmonary, Critical Care and Sleep Medicine in collaboration with Department of Biochemistry at Government Medical College and Hospital (GMCH), Chandigarh over a period of one and half years from December 2022 to May 2024. 54 patients of stable Chronic Obstructive Pulmonary Disease attending the Pulmonary Medicine Outpatient department (OPD) were enrolled in the study. Patients with chronic kidney disease; co-morbidities like obstructive sleep apnoea, interstitial lung disease, lung cancer, pneumonia; history of acute cardiovascular event in preceding 6 weeks; history of acute exacerbation of COPD in preceding 6 weeks were excluded from the study. Informed consent was obtained from all the patients. A detailed clinical history and clinical findings were recorded on a structured proforma at the time of enrolment. Patients having COPD were subjected to spirometry, Diffusing Capacity of Lung for carbon monoxide (DLCO) and body plethysmography for static lung volume measurement. These procedures were performed in the Pulmonary Function Testing Laboratory in the Department of Pulmonary, Critical Care and Sleep Medicine, GMCH-32, Chandigarh. Spirometry was performed using, Helios model no. 702/401, RMS, for estimation of FVC, FEV1, FEV1/FVC percentage. Body plethysmograpghy with DLCO was performed using, Medisoft-Belgium model no. BODYBOX. The spirometry and body plethysmography were performed in accordance with American Thoracic Society Guidelines (ATS). Diagnosis of COPD and assessment of severity was done according to the recent GOLD guidelines [1].

Blood samples from each participant were collected under aseptic precautions at the time of recruitment. Apart from routine investigations, 3ml blood sample was collected from each participant for measurement of FGF23. Blood sample was allowed to clot. Serum was separated using centrifugation and stored at -20 degrees Celsius. FGF23 levels were then estimated using ELISA kit. Levels were compared with severity of disease using spirometry and with DLCO and lung volumes. Relationship between FGF23 levels and serum phosphate levels was also evaluated.

Results

The mean age of study population (n=54) was 59.9 ± 11.6 years. Majority of participants were male (72.2%). Out of 54 participants, 70.4% were ever smokers, with mean pack years of 23.4 ± 14.1 years. Half of the study population (50%) had history of environmental exposure. Hypertension was the most common co-morbidity encountered, followed by diabetes and old treated pulmonary tuberculosis.

Majority of study participants had moderate COPD (50%), followed by severe (27.8%), mild (20.4%) and very severe (1.9%) grade. This grading was done on the basis of post bronchodilator FEV1 (% predicted) values, as per GOLD guidelines [1]. DLCO < 80% was observed in 40.7% of total study participants. Mean FGF23 in participants with DLCO < 80% was 165.4 ± 229.2 and in participants with DLCO > 80% was 80.3 ± 103.4. Descriptive analysis of all clinical and pulmonary variables is compiled in Table 1.

Correlation analyses between FGF23 and clinical and pulmonary variables is compiled in Table 2. Mean plasma FGF23 value observed was 115 ± 169 pg/ml. A statistically significant negative correlation was observed between FGF23 levels and FEV1 (% predicted) demonstrating diagnostic role of FGF23 ($p = 0.020$, $r = -0.3$). For every 1 unit increase in FEV1 %, the FGF 23 (pg/mL) decreased by 1.82 units. There was a moderate negative correlation between FVC % and FGF 23 (pg/mL), and this correlation was statistically significant ($p = 0.013$, $r = -0.3$).

The phosphaturic action of FGF23 was validated by a strong negative correlation observed between serum phosphate and plasma FGF23 levels ($p = <0.001$, $r = -0.6$). For every 1 unit increase in S. Phosphate, the FGF 23 (pg/mL) decreases by 122.6 units.

Negative correlation between FGF23 with inspiratory reserve volume (% predicted) and vital capacity (% predicted) was also observed. There was no correlation between FGF23 and expiratory reserve volume (% predicted).

No significant relation was seen between FGF23 and DLCO%. Distribution of FGF23 among different severity grades of COPD and GOLD stage was not statistically significant.

Serum phosphate levels were positively correlated with FEV1 % predicted ($p = 0.006$, $r = 0.4$) and FVC % predicted ($p = 0.009$, $r = 0.3$). No significant correlation was seen with serum phosphate and static lung volumes (Table 3).

ROC curve analysis of FGF23 showed that cut off levels of 73.71 pg/ml can be used to distinguish mild to moderate COPD from severe to very severe, with a sensitivity and specificity of 62.5% and 68.4% respectively (Table 4, Figure 1).

Discussion

This study aimed to evaluate FGF23 as a severity marker in COPD. A total of 54 cases of COPD diagnosed spirometrically (post bronchodilator FEV1/FVC < 70) were enrolled, as per the specified inclusion and exclusion criteria. Mean age of the study population was 59 ± 11 years (range 40 – 85 years). Out of the total study population, 72.2% were males. This gender distribution is consistent with findings of Aryal S et al which showed that COPD is more prevalent among males as compared to females [8].

Among the 54 participants, 70.4% were ever smokers and 29.6% were non-smokers. Out of smokers, 81.6% participants were male. Of 38 participants who were ever-smokers, the mean pack years was 23 ± 14 years. Also, distribution of participants with history of environmental exposure was equal. 50% of participants with history of biomass exposure, passive smoking or occupational exposure were included in this group. Smoking has been attributed as the most important etiology for COPD [9]. Other leading causes among non-smokers include biomass exposure, occupational exposure to dust and smoke, history of pulmonary tuberculosis, poor socio-economic status and outdoor air-pollution [10]. The current study included participants with almost all major etiological factors of COPD in order to provide more reliable data.

All participants were subjected to spirometry and body plethysmography with DLCO to assess lung functions. Based on post-bronchodilator FEV1 (% predicted) value, participants were categorised into Mild, Moderate, Severe and Very severe, as per GOLD guidelines.[1] Majority belonged to Moderate group (50%), followed by 27.8% in severe and 20.4% in Mild grade. Only 1.9% of participants belonged to the Very severe group. The static lung volumes and DLCO (%) were also assessed. The mean DLCO (%) was 82.2 ± 13.4 %. 40.7% of participants

had DLCO < 80%. Impaired diffusion capacity in COPD patients is an indicator of underlying emphysema and signifies a meaningful decline in exercise capacity [11].

Plasma FGF23 levels were measured by the commercially available ELISA kit. The mean FGF 23 measured was 115 ± 169 pg/ml. The distribution of plasma FGF23 levels among different grades of COPD severity was not significant. The mean FGF3 levels seen in Mild group were 65.75pg/ml; in Moderate group were 121 pg/ml; Severe group were 120.8 pg/ml and in Very severe group were 409.2 pg/ml. This may be attributed to smaller number of participants included in each group and the fact that all participants included were outpatient and only one had very severe COPD (as per GOLD guidelines) [1]. Also, FGF23 is a pro-inflammatory marker and its levels may be largely altered by various other factors. It is implicated in pathophysiology of various other disorders, which are under evaluation. Hence, it is not specific to COPD. Studies suggest that bone and mineral factors, iron status, erythropoeitin levels can affect FGF23 levels, but the role of FGF23 in these is still questionable [12]. To the best of our knowledge, we excluded individuals with chronic renal disease and acute cardiovascular disorders (within 6 weeks) to remove the known confounders [13-17].

Association of plasma FGF23 levels was studied with spirometry, static lung volumes and DLCO. The results in the present study showed a statistically significant moderate negative correlation of FGF23 with FEV1 observed, FEV1 % predicted and FVC % predicted. This signifies that FGF23 levels were found to be higher in individuals with poor lung functions. In the current study, a statistically significant moderately negative correlation of plasma FGF23 levels was established with inspiratory reserve volume (% predicted) and vital capacity (% predicted). Although no statistically significant correlation was found between FGF23 levels and expiratory reserve volume (% predicted). These findings validate the underlying physiological mechanism in obstructive lung diseases. Air trapping in COPD leads to significant increase in residual volume. This generates a higher positive pressure at the end of expiration. As a result, during inspiration, inspiratory capacity declines. This decline is attributed to a fall in the inspiratory reserve volume, whereas tidal volume remains almost same. Also, no change in expiratory reserve volume is observed in patients with COPD, as compared to normal individuals [18]. Some studies have also indicated that inspiratory capacity is a better indicator of severity of COPD, than FEV1 % predicted [19].

In our study, no statistically significant correlation of plasma FGF23 levels was observed with DLCO (%). This is in contrary to a study, which claims to be the first study to evaluate

association of FGF23 with DLCO [20]. According to them, a clinically significant correlation was established between FGF23 and DLCO %. The reason for such disparity lies in the fact that, DLCO % is found to be decreased in emphysematous phenotype of COPD, while it remains unaffected or within normal limits in airway-disease dominant phenotype. HRCT chest is warranted to identify the degree of emphysema and to correlate between the two [21].

Also, a statistically significant strong negative correlation was seen between FGF23 and serum phosphate levels, thus confirming the phosphaturic action of FGF23. For every 1 unit increase in serum phosphate, the FGF 23 (pg/mL) was found to decrease by 122.6 units.

Since hypophosphatemia is known to augment respiratory muscle failure, its association with lung functions was also studied [22]. A statistically significant moderate positive correlation of serum phosphate levels was established with FEV1 observed, FEV1 % and FVC % (Table 3). However, no clinically significant correlation was observed between serum phosphate levels and static lung volumes.

ROC curve analysis of FGF23 levels in current study showed that cut off levels of 73.71pg/ml can be used to predict COPD severity as severe – very severe with a sensitivity of 62%, and a specificity of 68% (Figure 1). Conversely, levels < 73.71pg/ml predict COPD severity as mild – moderate. The area under the ROC curve for FGF 23 predicting COPD severity was 0.625, thus demonstrating poor diagnostic performance. The diagnostic accuracy of FGF23 in predicting COPD came out to be 66.7% as per the current study. FGF23 holds a positive-predictive value of 45.5% and a negative predictive value of 81.2%. However, the validity of above results is questionable, owing to paucity of literature and smaller sample size.

The findings suggest an indirect role of FGF23 in COPD. In the present study, FGF23 has been demonstrated to be a potential cause of hypophosphatemia in COPD, by a statistically significant strong negative correlation between the two. Both plasma FGF23 and serum phosphate levels show statistically significant correlation with spirometrically determined lung functions. These findings imply, that FGF23 causes respiratory muscle failure and increase mortality, morbidity and hence, severity of COPD through hypophosphatemia. FGF23 is reflected as a cause of hypophosphatemia in COPD. Also, raised FGF23 levels cause serum phosphate levels to fall significantly, thus increasing severity of disease. On the other hand, FGF23 is a pro-inflammatory hormone. Its association with inflammation is ancient. Current studies also imply its role in aging. COPD is regarded as an inflammatory lung disorder, with higher prevalence in older age group. Joining the dots and the findings of our study, we infer

that FGF23 is anticipated to play a pivotal role in the pathophysiology of COPD. It can serve as a potential severity marker of the disease, which increases morbidity and mortality indirectly, by decreasing intestinal phosphate absorption, thus causing hypophosphatemia. Although, confirmation of these findings needs more scrutiny. Since this study was one of its kind, and with scarce data available in this area, the results of this study can pave a way for further research in this domain.

The current study had a few limitations. Firstly, inclusion of smaller number of participants in each grade of severity may have affected the power of study. Secondly, current literature is deficient in determining effects of pharmacology on FGF23 levels. It can be hypothesised that oral or inhaled corticosteroids may have detrimental effect on plasma FGF23 levels, and the same was not evaluated. Also long acting beta-agonists and long acting muscarinic agents may also have similar effects. Since all participants were already diagnosed cases of COPD, the ongoing treatment might have influenced the results. Thirdly, a few studies have shown a prognostic role of FGF23 levels in COPD [7]. The current study aimed at evaluating only the diagnostic power of FGF23. Lastly, our study did not include individuals with acute exacerbation. Only stable COPD from outpatient were included.

Conclusions

Research on diagnostic role of FGF23 in Chronic obstructive Pulmonary Disease is sparse. Plasma FGF23 levels were found to show a promising role as a severity marker of COPD. Phosphaturic action of FGF23 was also validated. FGF23 levels were found to be significantly increased in individuals with poor lung functions and compromised lung volumes. Low serum phosphate levels were also associated with poor lung functions. FGF23 levels were negatively correlated with FEV1 (% predicted) and can be used as a potential severity marker. However, further research and studies using larger sample size may help to validate these findings.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of COPD 2024. Available from: http://www.goldcopd.org/.
2. López-Campos JL, Tan W, Soriano JB. Global burden of COPD. Respirology 2016;21:14-23.

3. Hoesein FA, Zanen P, Lammers JW. Lower limit of normal or FEV1/FVC< 0.70 in diagnosing COPD: an evidence-based review. Respir Med 2011;105:907-15.
4. Kakavas S, Kotsiou OS, Perlikos F et al. Pulmonary function testing in COPD: looking beyond the curtain of FEV1. NPJ Prim Care Respir Med 2021;31:23.
5. Tilert T, Dillon C, Paulose-Ram R et al. Estimating the US prevalence of chronic obstructive pulmonary disease using pre-and post-bronchodilator spirometry: the National Health and Nutrition Examination Survey (NHANES) 2007–2010. Respir Res 2013;14:103.
6. Kuro-O M. The FGF23 and Klotho system beyond mineral metabolism. Clin Exp Nephrol 2017:64-9.
7. Gulati S, Wells JM, Urdaneta GP et al. Fibroblast growth factor 23 is associated with a frequent exacerbator phenotype in COPD: a cross-sectional pilot study. Int J Mol Sci 2019;20:2292.
8. Aryal S, Diaz-Guzman E, Mannino DM. COPD and gender differences: an update. Transl Res 2013;162:208-18.
9. Laniado-Laborín R. Smoking and chronic obstructive pulmonary disease (COPD). Parallel epidemics of the 21st century. Int J Environ Res Public Health 2009;6:209-24.
10. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet 2009;374:733-43.
11. Díaz AA, Pinto-Plata V, Hernández C et al. Emphysema and DLCO predict a clinically important difference for 6MWD decline in COPD. Respir Med 2015;109:882-9.
12. Hanudel MR, Laster M, Salusky IB. Non-renal-related mechanisms of FGF23 pathophysiology. Curr Osteoporos Rep 2018;16:724-9.
13. Faul C, Amaral AP, Oskouei B et al. FGF23 induces left ventricular hypertrophy. J Clin Invest 2011;121:4393-408.
14. Seiler S, Heine GH, Fliser D. Clinical relevance of FGF-23 in chronic kidney disease. Kidney Int Suppl 2009;76:S34-42.
15. Musgrove J, Wolf M. Regulation and effects of FGF23 in chronic kidney disease. Annu Rev Physiol 2020;82:365-90.
16. Lu X, Hu MC. Klotho/FGF23 axis in chronic kidney disease and cardiovascular disease. Kidney Dis 2017;3:15-23.

17. Stöhr R, Schuh A, Heine GH, Brandenburg V. FGF23 in cardiovascular disease: innocent bystander or active mediator? Front Endocrinol 2018;9:351.
18. Lutfi MF. The physiological basis and clinical significance of lung volume measurements. Multidiscip Respir Med 2017;12:1-2.
19. Yetkin O, Gunen H. Inspiratory capacity and forced expiratory volume in the first second in exacerbation of chronic obstructive pulmonary disease. Clin Respir J 2008;2:36-40.
20. Kraen M, Frantz S, Nihlén U, et al. Fibroblast growth factor 23 is an independent marker of COPD and is associated with impairment of pulmonary function and diffusing capacity. Respir Med 2021;182:106404
21. Kitaguchi Y, Fujimoto K, Kubo K, Honda T. Characteristics of COPD phenotypes classified according to the findings of HRCT. Respir Med 2006;100:1742-52.
22. Gravelyn TR, Brophy N, Siegert C, Peters-Golden M. Hypophosphatemia-associated respiratory muscle weakness in a general inpatient population. Am J Med 1988;84:870-6.

Table 1. Data on anthropometrics, pulmonary and clinical variables according to COPD status. Values are mean ± SD or numbers.

VARIABLES	
AGE (YEARS)	59.9 ± 11.6 years
GENDER (MALE/FEMALE)	39/15
BMI (Kg/m2)	25.3 ± 4.3
SMOKER (YES/NO)	38/16
PACK YEARS	23.4 ± 14.1 years
HYPERTENSION (YES/NO)	23/31
DIABETES (YES/NO)	13/41
OLD TREATED PTB (YES/NO)	11/43
S. PHOSPHATE	2.9 ± 0.67 mg/dl
FGF 23 (pg/ml)	115 ± 169 pg/ml
FEV1 (% pred)	59.7 ± 18%
FVC (% pred)	73 ± 16.2%
FEV1/FVC	59.2 ± 8.5
TIDAL VOLUME	556 ± 70 ml
INSPIRATORY RESERVE VOLUME (% pred)	73.6 ± 11.3
EXPIRATORY RESERVE VOLUME (% pred)	68 ± 12.8
INSPIRATORY CAPACITY	1935 ± 383 ml
EXPIRATORY CAPACITY	1363 ± 284 ml
VITAL CAPACITY (% pred)	83.7 ± 13.3
DLCO %	82.2 ± 13.4

Table 2. Correlation analyses between FGF23 and clinical and pulmonary variables in all subjects (n=54).

VARIABLE	**SPEARMAN CORRELATION COEFFICIENT**	**P VALUE**
AGE	-0.0	0.896
BMI	0.1	0,687
PACK YEARS	-0.1	0.402
S. PHOSPHATE	-0.6	<0.001
FEV1 (% pred)	-0.3	0.020
FVC (% pred)	-0.3	0.013
FEV1/FVC	-0.2	0.183
TIDAL VOLUME	0.1	0.304
IRV (% pred)	-0.5	<0.001
ERV (% pred)	-0.2	0.148
IC	-0.1	0.688
EC	-0.0	0.912
VITAL CAPACITY	-0.3	0.012
DLCO %	-0.1	0.354

Table 3. Correlation analyses between S. phosphate and clinical and pulmonary variables in all subjects (n=54).

VARIABLE	SPEARMAN CORRELATION COEFFICIENT	P VALUE
AGE	-0.0	0.948
BMI	0.1	0,344
PACK YEARS	0.2	0.165
FGF 23	-0.6	<0.001
FEV1 (% pred)	0.4	0.006
FVC (% pred)	0.3	0.009
FEV1/FVC	0.3	0.041
TIDAL VOLUME	-0.0	0.909
IRV (% pred)	0.2	0.128
ERV (% pred)	0.1	0.286
IC	-0.0	0.953
EC	0.0	0.991
VITAL CAPACITY	-0.0	0.956
DLCO %	-0.0	0.973

Table 4. Performance of FGF23 for predicting COPD severity.

Parameter	Value (95% CI)
Cutoff (p value)	73.71 (0.153)
AUROC	0.625 (0.454 - 0.796)
Sensitivity	62.5% (35-85)
Specificity	68.4% (51-82)
Positive Predictive Value	45.5% (24-68)
Negative Predictive Value	81.2% (64-93)
Diagnostic Accuracy	66.7% (53-79)
Positive Likelihood Ratio	1.98 (1.08-3.62)
Negative Likelihood Ratio	0.55 (0.28-1.07)
Diagnostic Odds Ratio	3.61 (1.06-12.25)

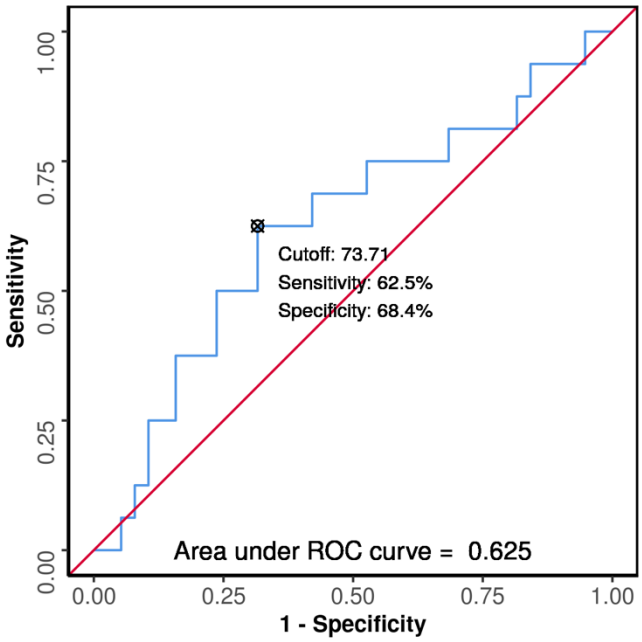

Figure 1. ROC curve analysis showing diagnostic performance of FGF 23 (pg/mL) in predicting COPD severity.