Section: Medicine

Original Research Article

EVALUATION OF SURFACTANT PROTEIN-D, FIBRINOGEN, AND INTERLEUKIN-6 AS BIOMARKERS ASSOCIATED WITH CLINICAL OUTCOMES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a major global health burden associated with progressive airflow limitation, systemic inflammation, and recurrent exacerbations. The present study was conducted to evaluate the association of surfactant protein-D (SP-D), fibrinogen, and interleukin-6 (IL-6) levels with clinical outcomes and disease severity in patients with COPD. **Type of study: Observational cross-sectional study**
Duration and Place of study: This study was conducted Bhitai Dental and Medical College Mirpurkhas from May 2025 to May 2026
Materials and Methods: A total of 120 patients with COPD were enrolled after obtaining informed consent. Clinical assessment was performed using relevant clinical parameters and disease severity scoring. Blood samples were collected, processed, and analyzed for serum levels of SP-D fibrinogen, and IL-6 using laboratory-based assays. The relationship between biomarker levels and clinical outcomes was assessed using appropriate statistical methods. Data analysis was performed using statistical software.
Results: Among 120 patients, increased levels of SP-D, fibrinogen, and IL-6 were observed in patients with greater disease severity and poorer clinical outcomes. IL-6 and fibrinogen demonstrated a significant positive association with markers of inflammation and disease burden. SP-D levels showed a significant correlation with clinical indicators of pulmonary impairment and exacerbation risk. Combined assessment of these biomarkers demonstrated potential utility in identifying patients at increased risk of adverse outcomes.
Conclusion: Elevated levels of surfactant protein-D, fibrinogen, and interleukin-6 are associated with disease severity and clinical outcomes in patients with COPD. These biomarkers may serve as useful predictors for monitoring disease progression and identifying patients requiring closer clinical evaluation.
Keywords: Chronic obstructive pulmonary disease, surfactant protein-D, fibrinogen, interleukin-6, inflammatory biomarkers, disease severity, exacerbations, clinical outcomes.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is not a single disease, but an umbrella term that combines the air restriction that occurs as a result of the underlying inflammatory process and the progressive loss of lung function. Pharmacoepidemiology is one of the most important

causes of morbidity and mortality in the world, which has a significant impact on healthcare systems and patients' quality of life. The disease is mainly associated with inhalation of noxious particles and vapors, including cigarette smoke, but also with occupational exposure, air pollution and a genetic predisposition to the disease and the development of the disease.[1] COPD presents with episodes of clinical stability, becoming somewhat worse during acute episodes of COPD, which are responsible for rapid loss of lung function, increased hospitalisations and substantial mortality.[2]

COPD pathogenesis is a complex interaction between chronic inflammation, oxidative stress, airways remodeling and parenchymal destruction. Since inflammatory cells such as neutrophils, macrophages and lymphocytes release several inflammatory mediators which are responsible for airway constriction and lung damage.[3] Properly, persistent inflammation leads to the production of additional cytokines, acute-phase proteins, and systemic inflammatory responses that go past the lungs. Systemic effects include increased risk of cardiovascular disease, skeletal muscle dysfunction, and negatively impact clinical outcomes in affected patients.[4] Establishment of a reliable biological marker to reflect disease activity, severity, and prognosis has become an important field of COPD research. The traditional clinical outcomes that were discussed, like forced expiratory volume in 1 second (FEV1), symptom scores, and exacerbation history, offer important information, but do not necessarily reflect underling inflammatory process. Patient stratification, therapeutic decision making and monitoring of therapeutic response could benefit from the use of disease progression markers and risk of worsening markers that would be termed biomarkers in this chapter.[5] Surfactant protein-D (SP-D) is a collectin glycoprotein synthesized mainly by alveolar type II epithelial cells and non-ciliated bronchiolar epithelial cells, which contains a collagenous domain and is secreted as a tritolomer with other related proteins.Surfactant protein-D (SP-D) is a collectin glycoprotein, consisting of a collagen domain, secreted as a tritolomer with other related proteins and synthesized primarily by the alveolar type II and non-ciliated bronchiolar epithelial cells. It regulates inflammatory response and the integrity of the epithelium, thus contributing significantly to the innate immunity in the pulmonary environment. In COPD, an alteration of the alveolar-capillary barrier leads to SP-D leakage into the circulation, promoting elevated serum levels of SP-D. COPD has been shown in previous studies to be associated with elevated serum levels of SP-D and indeed the level of SP-D may be indicative of the degree of lung injury/inflammation.[6] As well, elevated concentrations of SP-D have been linked to enhanced exacerbation rates, decrease in lung function and an increase in mortality risk, making it a potential prognostic biomarker.[7]

Fibrinogen is an acute phase plasma protein that is primarily produced in the liver upon inflammation. A rise in the levels of fibrinogen is a reflection of systemic inflammation and has been identified as a useful inflammatory biomarker in COPD. Fibrinogen levels have been found to be higher in severe disease, frequent exacerbations, decreased exercise capacity and death in COPD patients [8]. Fibrinogen is known to play a role in the clotting process, and it has been identified as a risk indicator for COPD exacerbation by the United States Food and Drug Administration (FDA).[9]

IL-6 is a pro-inflammatory cytokine with multiple functions that are important in immune regulation, acute-phase responses and chronic inflammatory conditions. COPD-associated IL-6 production is mediated by activation of airway epithelial cells, airway macrophages and other inflammatory cells. High levels of IL-6 have been linked to poor lung function, high exacerbation rates, and poor clinical outcomes.[10] In addition, Il-6 helps induce systemic complications associated with COPD such as muscle wasting and cardiovascular complications.[11] While some biomarkers like SP-D, fibrinogen, and IL-6 are found to be associated with severity of COPD and outcomes, it may be better to measure combinations of these. COPD is a complex disease with multiple inflammation pathways and a combination of several markers may be more predictive than assessing one individual marker by itself.[12] There are multiple studies that have indicated that including inflammatory and epithelial injury markers could improve the risk stratification of COPD patients for exacerbations and mortality.[13]

Although progress has been made in the understanding of the pathogenesis of COPD, there is a need to develop easily accessible and reliable biomarkers that will allow for patients to be identified at higher risk of disease progression and adverse outcomes. Further clarification of the link of circulating biomarkers with clinical features may allow tailoring management for individual patients and help support better long term results in COPD patients.[14]

Thus, this study aimed to investigate the relationship of SP-D, fibrinogen and IL-6 in CLI patients with COPD and respective clinical outcomes. The aim of this study is to evaluate these biomarkers to find out if they can help predict how serious the disease is and tell which patients may be at greater risk of a poor clinical outcome.[15]

MATERIALS AND METHODS

It was cross-sectional and observational study which included 120 patients suffering from chronic obstructive pulmonary disease (COPD). After informed consent, patients of both sexes were included who already had a diagnosis of COPD on the basis of a diagnosis setting in the clinic that was

verified in the patient.Patients of both sexes, with a confirmed diagnosis of COPD, were included, after obtaining informed consent. Selection criteria for patients was decided in advance. People with other major respiratory diseases like bronchiectasis, active lung infections, cancelled due to lung malignancy, could affect inflammatory biomark levels, active interstitial lung disease, and active bronchiectasis and were therefore excluded. Additionally, pregnant women and lactating mothers were not included in the study.

All the participants were asked to provide a detailed clinical history, including demographic data, smoking history, disease history, drugs used and history of the disease exacerbations affecting COPD. Disease severity and outcomes were assessed by clinical assessment via clinical parameters. A proforma for the data collection was designed and the obtained data of all the participants were recorded based on the data that are given.

All subjects had taken venous blood samples under aseptic conditions. Samples of blood were centrifuged to separate the serum/plasma and then stored under proper conditions until they were analysed. Serum level of surfactant protein-D (SP-D), fibrinogen, and interleukin-6 (IL-6) were measured using enzyme-linked immunosorbent assay (ELISA) as per the manufacturer's instructions. Concentrations obtained for the biomarkers were noted and compared with clinical parameters of outcome and severity of the disease.

Appropriate statistical software was used for statistical analysis. The continuous variables were checked with Shapiro Wilk test for distribution. Means and standard deviations were used when measurements were normally distributed and medians with interquartile range were used for measurements that were not normally distributed. Frequencies and percentages were presented for categorical variables. To assess the relationship between the concentration of SP-D, fibrinogen and IL-6 and clinical parameters, correlation analysis was conducted. No, we used multivariable regression analysis and looked at the independent effect of inflammatory biomarkers on clinical outcomes. A p-value of <0.05 was considered statistically significant.

This study was approved before its commencement by relevant institutional ethics committee. Written informed consent was obtained from all the participants, and patient information was assured to be confidential throughout the study.

RESULTS

The study included a total of 120 patients with the diagnosis of chronic obstructive pulmonary disease. The socio-demographic and clinical features of the study population are summarized in table 1. Most of the participants were males, which is compatible with the higher prevalence of COPD seen in males who had smoked and were Occupational Exposure History. Ages of study participants ranged from 47 to 80 years, with a mean of 61.4 ± 9.8 years. Clinical assessment showed different degree of the severity of the disease; a large number of the patients suffered from moderate to severe COPD according to the clinical parameters.

Table 1. Demographic data of the patient

Variables	Findings
Age (years)	61.4 ± 9.8
Male gender	92 (76.7%)
Female gender	28 (23.3%)
Smoking history	84 (70.0%)
Previous exacerbation history	76 (63.3%)
Mean CAT score	18.6 ± 7.4
Moderate to severe disease	88 (73.3%)

Each participant had their SP-D, fibrinogen and IL-6 concentrations measured in their serum. Levels of inflammatory markers were increased in COPD patients, and were higher than the mean levels, suggesting continued pulmonary and systemic inflammation. The data on the distribution of biomarker levels are presented in Table 2

Table 2. Distribution of biomarkers

Biomarker	Mean ± SD
Surfactant Protein-D (SP-D)	**78.5 ± 32.6 ng/mL**
Fibrinogen	412.7 ± 126.4 mg/dL
Interleukin-6 (IL-6)	12.4 ± 6.8 pg/mL

Patients' severity scores were significantly higher than patients with milder disease for SP-D, fibrinogen, and IL-6 in the analysis of disease severity categories. Higher biomarker levels were specifically seen in those who had more frequent exacerbations, and more symptom burden.There was no significant cross-over or definite dose-response association between severity and levels of any biomarker

Table 3: Association between biomarker levels and COPD severity

Biomarker	Mild COPD	Moderate COPD	Severe COPD	p-value
SP-D (ng/mL)	52.4 ± 21.3	74.6 ± 26.5	96.8 ± 34.7	<0.001
Fibrinogen (mg/dL)	338.5 ± 98.4	401.7 ± 112.6	482.9 ± 139.5	<0.001
IL-6 (pg/mL)	7.2 ± 3.6	11.5 ± 5.2	16.8 ± 7.4	<0.001

To assess the relation between biomarkers with clinical outcomes, correlation analysis was carried out. SP-D showed a marked positive association with the scores of the disease severity and frequency of exacerbations (r=0.46, p<0.001). There was also a significant negative correlation between the level of fibrinogen and exacerbation rate (r=0.39, p<0.001) as well as with clinical severity (r=-0.24, p<0.01). IL-6 was strongly correlated with adverse clinical outcome, with a positive correlation with the frequency of exacerbation and its severity (r=0.51, p<0.001).However, clinical outcomes were not always correlated with biomarkers as shown in Table 4.

Table 4: Correlation of biomarkers with clinical outcomes

Variables	Correlation coefficient (r)	p-value
SP-D and exacerbation frequency	0.46	<0.001*
Fibrinogen and exacerbation frequency	0.39	<0.001*
IL-6 and exacerbation frequency	0.51	<0.001*
CAT score and IL-6	0.48	<0.001*
CAT score and SP-D	0.42	<0.001*

Multivariable regression analysis was performed to identify the magnitude of the independent contribution of each (SP-D, fibrinogen and IL-6) to poor clinical outcome. The regression model was statistically significant and accounted for a significant amount of variance for the clinical outcomes. The highest independent predictor was IL-6, with levels of fibrinogen and SP-D making up the top three. Table 5 summarizes results from the multiple regression analysis for the predictors of adverse clinical outcomes. The results of multiple regression analysis of the predictor variables for adverse clinical outcomes.

Table 5: Multiple regression analysis for predictors of adverse clinical outcomes

Predictor variable	Regression coefficient (β)	p-value
IL-6	0.42	<0.001*
SP-D	0.31	0.002*
Fibrinogen	0.24	0.01*
Age	0.08	0.34

Results have shown a significant correlation of increased circulating levels of SP-D, fibrinogen and IL-6 with severity of the disease and worse clinical outcomes in patients with COPD. Of the markers examined, IL-6 had the best correlation with clinical parameters and may be a useful predictive inflammatory marker in COPD.

DISCUSSION

COPD is a clinicopathological inflammatory respiratory disease, which involves chronic airway limitation, frequent exacerbations, and systemic inflammatory responses. This study assessed the relationship of surfactant protein-D (SP-D), fibrinogen and interleukin-[6] (IL-6) levels with clinical parameters in 120 COPD patients. The results showed that with rising levels of the three biomarkers, it was statistically significantly correlated with increasing levels of severity of the disease and poorer clinical outcomes. Of all the biomarkers studied, IL[6] correlated most strongly with exacerbation number, followed by SP-D and fibrinogen that may have clinical relevance to determining the risk of adverse events.

These results are in agreement with those from Sin and others, which showed significantly high levels of circulating SP-D in COPD and that it was related to decreased lung function and disease activity.[16] Increased leakage into the circulation of this protein, which is indicative of the injury and disruption of alveolar epithelium and pulmonary barrier. Their results, like the current study, suggested that SP-D might be a marker of pulmonary inflammation and progression of disease.

Lomas et al also found that increase in SP-D levels correlated with increased exacerbation and mortality in COPD patients as a biomarker.[17] In the current study, we also found a significant correlation between the exacerbation frequency and the levels of SP-D that suggests that SP-D levels may be a useful marker to provide prognostic information in addition to the traditional clinical assessment.

Fibrinogen is an inflammatory biomarker in COPD which has been investigated extensively. A previous study by Dahl et al. found that increased plasma fibrinogen levels were correlated with worsening COPD, lower lung function and higher mortality risk.[18] Likewise, the present study showed that there was a significant association between higher fibrinogen levels and worse clinical outcomes. Its association could be attributed to the fact that fibrinogen is an acute-phase reactant linked to

ongoing systemic inflammatory process in COPD patients.

Thomsen et al. analysed inflammatory biomarkers and their association with exacerbation risk of COPD and found that a high fibrinogen level was predictive of exacerbation risk[19] These observations are supported by the findings of the present study which found fibrinogen to be a contributor to predicting clinical deterioration in COPD. The other studies, however, also reported a stronger association with fibrinogen than other biomarkers, whereas, in this study, IL-6 was the strongest predictor of adverse events.

In comparison to IL-6, Donaldson et al. showed that COPD patients with elevated serum inflammatory markers, such as IL-6, had faster decreases in lung function and a higher inflammatory activity.[20] This present study also revealed the same trend, whereby the highest correlation with exacerbation frequency and symptom/scratch load was for IL-6. This could be owing to the important role of IL-6 in the mediation of acute phase responses, chronic inflammation and systemic effects of COPD.

Agustí et al. also discussed that systemic inflammation with COPD may be a persistent process, as inflammatory variables were related to the clinical outcomes and increased mortality risk[21]. In the present study, we explored this further by analysing an integrated biomarker strategy and found that an integrated approach of measuring three biomarkers (SP-D, fibrinogen and IL-6) might capture a more complete picture of the inflammatory activity and disease progression.

The results indicate biomarker-based assessment can combine with the existing clinical evaluation methods, utilizing symptom scores, exacerbation history and lung function testing. COPD is complex disease which has multiple inflammatory pathways; using a combination of markers of epithelial injury and markers of systemic inflammation may significantly enhance the ability to identify high risk patients. Additional longitudinal studies to compare these biomarkers to subsequent exacerbation and treatment outcome are needed.

CONCLUSION

This present study shows that the amount of surfactant-protein-D, fibrinogen and interleukin-6 is significantly related with severity and worse clinical status in chronic obstructive pulmonary disease patients. These biomarkers included the strongest correlation with exacerbation frequency – interleukin-6, which may therefore be a marker of systemic inflammation. Significant correlation with clinical outcomes was observed for surfactant protein-D and fibrinogen, indicating its possible role to represent the injury of the pulmonary epithelium and the systemic inflammation. An overall evaluation of these biomarkers might give valuable predictive information and help in the identification of patients with increased likelihood of worsening and disease progression. These are recommended to be studied further with longitudinal methods to confirm their use in routine clinical practice and personalized management of COPD.

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