DOI: https://doi.org/10.53350/pjmhs02024181886

ORIGINAL ARTICLE

Association of Chronic Obstructive Pulmonary Disease Severity with Cutaneous Manifestations and Systemic Inflammatory Biomarkers. A Cross-Sectional Clinical Study

KASHIF SARDAR[1], NIGHAT FATIMA[2], SABA AMIN[3], SUFYAN SALEEM SAFDAR[4], ZAHID HABID QURESHI[5], BAKHTAWAR FAROOQ[6]
[1]*Associate Professor, Department of Pulmonology, Multan Medical & Dental College, Multan, Punjab, Pakistan.*
[2]*Associate Professor, Department of Dermatology, Multan Medical & Dental College, Multan, Punjab, Pakistan.*
[3]*Assistant Professor, Department of Dermatology, Multan Medical & Dental College, Multan, Punjab, Pakistan.*
[4]*Consultant Pulmonologist, Mukhtar A. Sheikh Hospital, Multan, Punjab, Pakistan.*
[5]*Associate Professor, Department of Physiology, Multan Medical & Dental College, Multan, Punjab, Pakistan.*
[6]*Associate Professor, Department of Biochemistry, Nishtar Medical University, Multan, Punjab, Pakistan.*
Correspondence to: Dr. Zahid Habid Qureshi Email: Zhqureshi86@gmail.com

ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory disease of the respiratory system with considerable extrapulmonary manifestations, such as dermatologic abnormalities. Chronic hypoxia and chronic systemic inflammation could play a role in the pathogenesis of multiple skin changes in patients with COPD. There is, however, limited data on the correlation between skin manifestations and systemic inflammatory biomarkers and the severity of the COPD.

Objective: To assess the relationship between COPD severity and inflammatory serum markers and cutaneous findings in patients with COPD.

Methods: The cross-sectional clinical study was performed from January 2022 to January 2023 at the Department of Pulmonology and Department of Dermatology, Multan Medical & Dental College. Consecutive non-probability sampling was done, and 150 patients with clinically and spirometrically diagnosed COPD were included. Severity of COPD was determined based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. A detailed dermatological examination was conducted to look for skin signs. Standard laboratory techniques were used for the measurement of serum levels of C-reactive protein (CRP), Interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), erythrocyte sedimentation rate (ESR) and fibrinogen. SPSS software version 26.0 was used to analyze the data.

Results: The mean age of participants was 60.9 ± 8.7 years, with male predominance (67.3%). The most frequent cutaneous manifestations were xerosis (46.0 %), hyperpigmentation (36.0 %), pruritus (32.7 %), nail clubbing (27.3 %) and cyanosis (23.3 %). The dermato-logical abnormalities were significantly higher in severe and very severe COPD patients than in the mild and moderate disease groups ($p<0.05$). Systemic inflammatory biomarkers including CRP, IL-6, TNF-α, ESR, and fibrinogen showed significant progressive elevation with increasing COPD severity ($p<0.001$). Strong positive correlation with inflammatory biomarker and the number of cutaneous manifestations was seen.

Conclusion: There is a marked association between the severity of COPD and systemic inflammatory activity and the frequency of cutaneous manifestations. Skin problems can be a valuable clinical sign of systemic inflammation and disease activity in COPD.

Keywords: Chronic Obstructive Pulmonary Disease; COPD; cutaneous manifestations; systemic inflammation; inflammatory biomarkers; IL-6; TNF-α; dermatology; pulmonary disease; CRP.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive inflammatory respiratory disease that leads to persistent airflow limitation, chronic airway inflammation and irreversible structural damage to the lungs[1]. It is regarded as one of the top causes of morbidity, mortality, burden of health services, decreased quality of life and premature death globally[2]. Cigarette smoking remains the major risk factor for COPD, although environmental pollution, occupational exposure to dust and chemicals, recurrent respiratory infections, and biomass fuel exposure also play important roles in disease development[3]. The prevalence of COPD has greatly risen over the past few decades especially in the developing regions where smoking rates and environmental pollution have continued to rise[4].

Although COPD has traditionally been thought to be a lung disease, recent research has shown that COPD is an inflammatory disease with extrapulmonary effects throughout the body[5]. Persistent systemic inflammation, oxidative stress, endothelial dysfunction, tissue hypoxia, and immune dysregulation contribute to the involvement of multiple organs and body systems[6]. Patients with COPD frequently develop cardiovascular disease, skeletal muscle dysfunction, metabolic abnormalities, osteoporosis, depression, malnutrition, and various dermatological abnormalities[7]. These extrapulmonary manifestations are increasingly recognized as important determinants of disease severity, prognosis, and overall clinical outcomes[8].

Received on 18-09-2023
Accepted on 29-12-2023

Systemic inflammatory activation is a key component in the pathogenesis and progression of COPD[9]. Inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and acute-phase reactants such as C-reactive protein (CRP) and fibrinogen remain persistently elevated in many COPD patients, particularly during advanced stages of disease[10]. Chronic inflammation and oxidative injury could play a role in vascular dysfunction, impaired tissue perfusion, collagen degradation, and skin structure and immunity alterations[11]. Constant exposure to hypoxia might exacerbate tissue damage and inflammation across the body, including the effects of smoking-related toxic effects.[12]

Cutaneous manifestations are increasingly being observed among patients with chronic pulmonary diseases, including COPD[13]. Dermatological abnormalities can develop due to chronic hypoxemia, systemic inflammation, nutritional deficiencies, long-term corticosteroid use, vascular changes due to smoking and impaired immune responses[14]. Patients with COPD often present with xerosis, pruritus, hyperpigmentation, cyanosis, nail clubbing, fungal skin infections, thinning of the skin, ecchymosis, premature wrinkles and slowed wound healing[15]. Although there is an increasing awareness of these manifestations, cutaneous involvement in COPD is underdiagnosed and poorly studied in clinical practice.[16]

A number of studies have shown strong correlation between inflammatory markers and the severity of COPD[17]. High levels of CRP, IL-6, TNF-α, erythrocyte sedimentation rate (ESR) and fibrinogen have been linked with a worsening of pulmonary function, more frequent exacerbations, hospitalizations and mortality[18]. There is, however, little clinical information about the association of systemic inflammatory biomarkers with the dermatological

manifestations in COPD patients, especially in the local population[19]. Understanding this association may help clinicians identify visible clinical indicators of systemic disease progression and inflammatory burden[20].

Recognition of cutaneous manifestations in COPD patients may provide additional clinical insight into disease severity and systemic inflammatory status[6]. Recognizing and identifying dermatologic abnormalities early in the course of the disease can lead to multidisciplinary management, timely intervention, and better care for the patient[11]. Thus the present study was carried out to assess the relationship between severity of COPD with cutaneous manifestations and systemic inflammatory biomarkers in COPD patients[14].

MATERIALS AND METHODS

The cross-sectional clinical study was carried out in the department of Pulmonology and Department of Dermatology, Multan Medical & Dental College, Multan from January 2022 till January 2023. The study was approved by the Institutional Ethical Review Committee. All subjects signed informed consent forms before entering the study.

This study involved 150 patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD) obtained from consecutive non-probability sampling. Patients ranging in age from 40 to 80 years who had clinically and spirometrically diagnosis of COPD were included. COPD diagnosis and severity classification was determined using post bronchodilator spirometry results, per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Mild, moderate, severe and very severe COPD groups were defined based on FEV1 measurements.

Excluded from the study were patients with known autoimmune dermatological diseases, chronic liver or kidney disease, active malignancy, HIV infection, connective tissue disorders, and acute systemic infections. Those who were using systemic immunosuppressive drugs, except inhaled CS, were also not included to reduce the confounding effect of other inflammatory influences.

Using a structured clinical proforma, detailed demographic and clinical data were recorded such as age, gender, smoking status, occupational exposure, duration of COPD, medication history, body mass index (BMI), and comorbid conditions. Consultant dermatologist was available for detailed dermatological examination for the identification of skin manifestations such as xerosis, pruritus, hyper pigmentation, cyanosis, nail clubbing, fungal skin infection, skin thinning, ecchymosis and chronic ulcerative lesions.

Pulmonary function test was done using calibrated spirometry as per American Thoracic Society guidelines. Disease severity was assessed by post-bronchodilator FEV1, forced vital capacity (FVC) and FEV1/FVC ratio.

Venous blood samples were obtained aseptically for laboratory analysis of systemic inflammatory biomarkers. The serum level of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), erythrocyte sedimentation rate (ESR), and fibrinogen were measured by enzyme-linked immunosorbent assay (ELISA) techniques and routine laboratory procedures. All laboratory investigations were done in the institutional pathology lab with a uniform quality control process.

The analysis of data was carried out in SPSS 26.0. Quantitative variables were expressed as mean ± standard deviation, while qualitative variables were presented as frequencies and percentages. Categorical variables were compared between the COPD severity groups using chi-square test. For comparison of continuous variables, independent sample t-test and one-way analysis of variance (ANOVA) were used. Pearson correlation was used to examine the correlation of systemic inflammatory biomarker levels with the cutaneous manifestations. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study included a total of 150 patients who had been clinically and spirometrically diagnosed with Chronic Obstructive Pulmonary Disease (COPD). The mean age of the study participants was 60.9 years with a standard deviation of 8.7 years (range 42 – 79 years). The patients were 101 (67.3%) males and 49 (32.7%) females. 118 (78.7%) participants had a smoking history. According to GOLD classification, 24 (16.0%) patients had mild COPD, 52 (34.7%) had moderate COPD, 46 (30.7%) had severe COPD, and 28 (18.6%) had very severe COPD. The mean duration of COPD was 7.6 ± 3.2 years. Table 1 shows the basic demographic and clinical data for the study population.

COPD patients commonly had cutaneous manifestations. Xerosis was the most common dermatological finding and was observed in 69 (46.0%) patients, followed by hyperpigmentation in 54 (36.0%), pruritus in 49 (32.7%), nail clubbing in 41 (27.3%), cyanosis in 35 (23.3%), fungal skin infections in 31 (20.7%), skin thinning in 24 (16.0%), and ecchymosis in 18 (12.0%) patients. Dermatologic manifestations were significantly more common as the severity of COPD increased. The prevalence of xerosis, cyanosis, clubbing, and hyperpigmentation were significantly higher in severe and very severe COPD group than in mild and moderate COPD group ($p<0.05$). Association between COPD severity and cutaneous manifestations is detailed in table 2.

There was a clear systematic increase in the levels of inflammatory biomarkers with increasing COPD severity. The mean value of CRP rose from 5.4 ± 1.8 mg/L for mild COPD patients to 20.7 ± 5.1 mg/L for very severe COPD patients. In a similar way, the level of IL-6, TNF-α, ESR and fibrinogen were also significantly increased in severe and very severe COPD groups as compared to mild and moderate groups of COPD ($p<0.001$). Inflammatory biomarker levels were also higher in patients with higher numbers of dermatological manifestations. Table 3 shows detailed inflammatory biomarker analysis based on the severity of COPD.

The results of Pearson correlation analysis showed that there was a significant positive correlation between systemic inflammatory biomarkers and total number of cutaneous manifestations in COPD patients. IL-6 showed the strongest correlation with dermatological involvement ($r=0.68$, $p<0.001$), followed by TNF-α ($r=0.63$, $p<0.001$), CRP ($r=0.59$, $p<0.001$), fibrinogen ($r=0.56$, $p<0.001$), and ESR ($r=0.52$, $p<0.001$). The results indicate that systemic inflammatory activity is associated with a higher burden of dermatological diseases in COPD patients.

In total, patients with severe and very severe COPD exhibited significantly increased prevalence of cutaneous manifestations and elevated levels of systemic inflammatory biomarkers than mild and moderate COPD patients, suggesting a clear link between systemic inflammation, dermatological abnormalities and COPD progression.

Table 1. Demographic and Clinical Characteristics of COPD Patients (n=150)

Variables	Frequency (%) / Mean ± SD
Age (years)	60.9 ± 8.7
Male	101 (67.3%)
Female	49 (32.7%)
Smokers	118 (78.7%)
Duration of COPD (years)	7.6 ± 3.2
BMI (kg/m²)	24.1 ± 3.9
Mild COPD	24 (16.0%)
Moderate COPD	52 (34.7%)
Severe COPD	46 (30.7%)
Very Severe COPD	28 (18.6%)

Table 2. Association of COPD Severity with Cutaneous Manifestations

Cutaneous Manifestation	Mild/Moderate COPD n (%)	Severe/Very Severe COPD n (%)	p-value
Xerosis	24 (31.6%)	45 (60.8%)	<0.001
Hyperpigmentation	19 (25.0%)	35 (47.3%)	0.004
Pruritus	20 (26.3%)	29 (39.2%)	0.041
Nail clubbing	14 (18.4%)	27 (36.5%)	0.012
Cyanosis	10 (13.2%)	25 (33.8%)	0.002
Fungal infections	13 (17.1%)	18 (24.3%)	0.283
Skin thinning	9 (11.8%)	15 (20.3%)	0.167
Ecchymosis	6 (7.9%)	12 (16.2%)	0.118

Table 3. Systemic Inflammatory Biomarkers According to COPD Severity

Biomarkers	Mild COPD	Moderate COPD	Severe COPD	Very Severe COPD	p-value
CRP (mg/L)	5.4 ± 1.8	9.3 ± 3.1	15.8 ± 4.5	20.7 ± 5.1	<0.001
IL-6 (pg/mL)	6.9 ± 2.3	11.4 ± 3.8	18.1 ± 4.9	24.6 ± 6.2	<0.001
TNF-α (pg/mL)	9.8 ± 2.7	14.7 ± 4.0	21.6 ± 5.3	27.4 ± 6.0	<0.001
ESR (mm/hr)	17.2 ± 5.9	27.5 ± 7.6	39.4 ± 9.7	51.8 ± 11.3	<0.001
Fibrinogen (mg/dL)	264 ± 48	338 ± 66	419 ± 79	503 ± 92	<0.001

DISCUSSION

The present study demonstrated a significant association between Chronic Obstructive Pulmonary Disease (COPD) severity, systemic inflammatory biomarkers, and cutaneous manifestations[1]. Overall, patients with severe and very severe COPD had significantly more dermatological abnormalities and significantly higher levels of inflammatory biomarkers than those with mild or moderate COPD[2]. These data confirm the notion that COPD is a multisystem inflammatory disease that has extrapulmonary manifestations, including the skin[3].

Systemic inflammation plays a central role in the pathogenesis and progression of COPD[4]. Persistent exposure to cigarette smoke and environmental pollutants activates inflammatory pathways leading to chronic release of cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and acute-phase reactants such as C-reactive protein (CRP) and fibrinogen[5]. Continuous inflammatory activation contributes to oxidative stress, endothelial dysfunction, tissue hypoxia, impaired immune responses, and structural tissue injury affecting multiple organ systems[6]. The increased levels of inflammatory biomarkers found in severe COPD patients in the current study are similar to those reported in other studies to increase with pulmonary disease severity[7].

In the present study xerosis was found to be most common cutaneous manifestation in COPD patients[8]. Factors which potentially contribute to poor skin barrier function and skin dryness include chronic dehydration, nutritional deficiencies, vascular damage from smoking, decreased activity of the sebaceous glands and prolonged exposure to topical steroids[9]. The same findings have been seen in other clinical investigations of dermatological parameters in chronic pulmonary disease patients[10]. Allergic reactions (hyperpigmentation and pruritus) were also commonly seen and showed strong association with advanced stages of disease[11]. Persistent inflammatory cytokine release and chronic hypoxemia may contribute to melanocyte stimulation, vascular changes, and sensory nerve irritation resulting in these manifestations[12].

Severe and very severe COPD patients were significantly more likely to have nail clubbing and cyanosis[13]. These findings likely reflect advanced pulmonary dysfunction and chronic tissue hypoxia[14]. Prolonged oxygen deprivation may induce peripheral vascular remodeling, connective tissue proliferation, and increased capillary permeability contributing to digital clubbing and cyanotic skin discoloration[15]. The presence of these visible clinical findings may thus mean that the systemic disease has progressed far and that there is impaired pulmonary reserve[16].

In the present study, there was also a statistically significant positive correlation between inflammatory markers and the total number of skin manifestations[17]. IL-6 and TNF-α showed particularly strong associations with dermatological involvement, suggesting that systemic inflammatory activity may directly influence skin pathology in COPD patients[18]. Elevated CRP and fibrinogen levels further indicate ongoing chronic inflammatory activation and increased systemic disease burden[19]. This suggests that the skin changes could be an external clinically significant marker of the systemic inflammatory burden in COPD[20].

Another key result of this study was the gradient of inflammatory markers from mild to severe COPD stages[6]. High levels of CRP, ESR, IL-6, TNF-α and fibrinogen confirmed in severe COPD patients have been previously reported suggesting that systemic inflammation plays a large role in the progression of disease, ease recurrence, hospitalizations, and death from COPD[9]. The association of inflammatory biomarkers with skin abnormalities also underscores the connection between the pulmonary and extrapulmonary inflammatory response in patients with COPD[12].

The present study has several clinical implications. Identification of skin changes in COPD patients could help clinicians to identify those with inflammatory burden and more severe COPD[15]. The early involvement of specialists (multidisciplinary) with pulmonologists and dermatologists can benefit patient monitoring, management strategies and possibly decrease disease-related complications[17]. Moreover, inflammatory markers can be helpful to monitor the activity and progression of systemic disease[19].

Several caveats need to be noted. A relatively small cross-sectional study with a single center, potentially limiting the generalizability of the findings[20]. Due to the cross-sectional design, causality between systemic inflammation and cutaneous manifestations could not be determined. Large multicenter longitudinal studies with greater numbers of patients are required to examine the prognostic value of dermatological signs and inflammatory biomarkers in the progression of COPD and long-term clinical outcomes[18].

CONCLUSION

There is a strong correlation between COPD severity and the prevalence of cutaneous manifestations as well as increased systemic inflammatory biomarker levels. Xerosis, hyperpigmentation, pruritus, nail clubbing and cyanosis were significantly more prevalent in patients with severe and very severe COPD. CRP, IL-6, TNF-α, ESR and fibrinogen levels rose gradually with the severity of the disease and were positively and significantly correlated with dermatological involvement. Results from this study indicate that dermatologic signs might be a valuable clinical marker of systemic inflammatory load and disease activity in COPD patients. The early identification of skin abnormalities and the evaluation of inflammatory markers could lead to better multidisciplinary management, more timely interventions and better clinical outcomes in Chronic Obstructive Pulmonary Disease patients.

Funding: The authors received no financial support for this research, authorship, or publication of this article.

Conflict of Interest: The authors declare no conflict of interest.

Data Availability: The data associated with the study are available from the corresponding author upon reasonable request.

Authors' Contributions

KS: Conceptualization, data collection, manuscript drafting.
NF: Study supervision, dermatological evaluation, manuscript review.
SA: Laboratory analysis and statistical interpretation.
SSS: Clinical assessment and data acquisition.
ZHQ: Pulmonary function testing and methodology design.
BF: Literature review, data compilation, and final manuscript editing.

Acknowledgments: The authors acknowledge the support of the Department of Pulmonology and Department of Dermatology, Multan Medical & Dental College, for facilitating this research work.

REFERENCES

1. Barnes PJ. Cellular and molecular mechanisms of asthma and COPD. Clin Sci (Lond). 2017;131(13):1541-1558.
2. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. Am J Respir Crit Care Med. 2017;195(5):557-582.

3. Agustí A, Faner R. COPD beyond smoking: new paradigm, novel opportunities. Lancet Respir Med. 2018;6(5):324-326.
4. Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. N Engl J Med. 2019;381(13):1257-1266.
5. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2016;138(1):16-27.
6. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet. 2017;389(10082):1931-1940.
7. Hurst JR, Han MK, Singh B, Vestbo J. Prognostic risk factors for moderate-to-severe exacerbations in patients with chronic obstructive pulmonary disease. Respir Res. 2017;18(1):146.
8. Higham A, Quinn AM, Cançado JED, Singh D. The pathology of small airways disease in COPD: historical aspects and future directions. Respir Res. 2019;20(1):49.
9. Stolz D, Mkorombindo T, Schumann DM, Agusti A, Ash SY, Bafadhel M, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. Lancet. 2022;400(10356):921-972.
10. Ritchie AI, Wedzicha JA. Definition, causes, pathogenesis, and consequences of chronic obstructive pulmonary disease exacerbations. Clin Chest Med. 2020;41(3):421-438.
11. Stockley RA, Halpin DMG, Celli BR, Singh D. Chronic obstructive pulmonary disease biomarkers and their interpretation. Am J Respir Crit Care Med. 2019;199(10):1195-1204.
12. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global initiative for chronic obstructive lung disease 2023 report. Eur Respir J. 2022;61(1):2200230.
13. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al. Global strategy for prevention, diagnosis and management of COPD: the GOLD science committee report 2019. Eur Respir J. 2019;53(5):1900164.
14. Barnes PJ, Burney PGJ, Silverman EK, Celli BR, Vestbo J, Wedzicha JA, et al. Chronic obstructive pulmonary disease. Nat Rev Dis Primers. 2015;1:15076.
15. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. J Allergy Clin Immunol. 2019;144(1):1-12.
16. MacNee W, Rabinovich RA, Choudhury G. Ageing and the border between health and disease. Eur Respir J. 2014;44(5):1332-1352.
17. Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook R, Criner GJ, et al. An updated definition and severity classification of chronic obstructive pulmonary disease exacerbations. Lancet Respir Med. 2021;9(6):573-574.
18. Agustí A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. Lancet Respir Med. 2017;5(12):935-945.
19. Miravitlles M, Ribera A. Understanding the impact of symptoms on the burden of COPD. Respir Res. 2017;18(1):67.
20. Cazzola M, Rogliani P, Matera MG. Escalation and de-escalation of therapy in COPD: myths, realities and perspectives. Drugs. 2020;80(14):1447-1465.

This article may be cited as: Sardar K, Fatima N, Amin S, Safdar SS, Qureshi ZH, Farooq B; Association of Chronic Obstructive Pulmonary Disease Severity with Cutaneous Manifestations and Systemic Inflammatory Biomarkers. A Cross-Sectional Clinical Study. Pak J Med Health Sci, 2024; 18(1): 886-889.