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Inflammatory and Metabolic Biomarkers as Objective Indicators of Chronic Pain in Patients with Pulmonary Diseases

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ABSTRACT

Chronic pain is a frequent but under-recognized complication in patients with chronic pulmonary diseases, often assessed subjectively and inconsistently. Increasing evidence suggests that systemic inflammation and metabolic dysregulation may contribute to pain perception; however, objective biomarkers remain insufficiently explored. The objective of this study was to evaluate inflammatory and metabolic biomarkers as objective indicators of chronic pain severity in patients with pulmonary diseases. In this experimental study, 180 participants (120 pulmonary disease patients with chronic pain and 60 healthy controls) were recruited. Pain intensity was assessed using the Visual Analog Scale (VAS), while serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), fasting glucose, insulin, and HOMA-IR were measured using standardized assays. Patients exhibited significantly elevated CRP (6.42 ± 1.18 mg/L vs. 1.92 ± 0.54 mg/L, $p < 0.001$), IL-6 (14.6 ± 3.9 pg/mL vs. 4.1 ± 1.2 pg/mL, $p < 0.001$), and TNF-α (18.3 ± 4.7 pg/mL vs. 7.2 ± 2.0 pg/mL, $p < 0.001$). Metabolic indices including HOMA-IR were also significantly higher in patients (3.12 ± 0.86 vs. 1.41 ± 0.39, $p < 0.001$) and positively correlated with VAS scores ($r = 0.61–0.74$). These findings demonstrate that inflammatory and metabolic biomarkers provide sensitive and objective indicators of chronic pain in pulmonary disease patients, supporting their potential role in rapid clinical pain assessment and monitoring.

Keywords: *Chronic pain, Pulmonary disease, Inflammatory biomarkers, Metabolic dysregulation, Objective pain assessment*

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INTRODUCTION

Chronic pulmonary diseases such as chronic obstructive pulmonary disease (COPD), interstitial lung disease, and bronchiectasis represent a major global health burden, characterized by progressive airflow limitation, persistent inflammation, and systemic complications [1]. While respiratory symptoms dominate clinical management, extrapulmonary manifestations including chronic pain increasingly affect patient quality of life and functional capacity [2].

Chronic pain in pulmonary disease patients is multifactorial, arising from musculoskeletal strain, hypoxia-induced neural sensitization, and systemic inflammation [3]. Despite its high prevalence, pain assessment remains largely subjective, relying on self-reported scales that may be influenced by psychological, cultural, and cognitive factors [4]. This subjectivity limits accurate monitoring and timely intervention.

Emerging evidence suggests that systemic inflammation plays a central role in pain modulation through cytokine-mediated sensitization of nociceptive pathways [5]. Pro-inflammatory mediators such as CRP, IL-6, and TNF-α have been implicated in both pulmonary pathology and chronic pain syndromes, indicating a shared biological mechanism [6]. Similarly, metabolic dysregulation and insulin resistance have been associated with enhanced pain perception and chronic inflammatory states [7].

Despite these insights, limited experimental studies have simultaneously evaluated inflammatory and metabolic biomarkers as objective indicators of chronic pain specifically in pulmonary disease populations. The lack of integrated biomarker-based assessment represents a significant gap in current clinical practice.To date, no clinical investigation exists that can objectively measure pain independently of patient self-report, and assessment in both practice and research continues to rely primarily on subjective tools such as the Visual Analog Scale, Numerical Rating Scale, and verbal rating scales. While these instruments are simple and widely used, they are limited by their focus on pain intensity, variability between individuals, and susceptibility to cognitive, emotional, and contextual influences, and they do not distinguish between different pain mechanisms such as nociceptive, neuropathic, or nociplastic pain, restricting their use for mechanism-based diagnosis and treatment. Multidimensional tools, including the McGill Pain Questionnaire and other composite measures, attempt to address these limitations by capturing sensory, affective, and evaluative dimensions, but they remain dependent on subjective reporting and are often impractical for routine clinical use due to increased respondent burden, time constraints, and interpretation challenges, making them more suitable for research than real-time clinical decision-making. Advanced neuroimaging techniques, such as functional MRI, PET, and EEG, have improved understanding of central pain processing, neuroplasticity, and sensitization in chronic pain, yet their application is largely confined to specialized research settings due to cost, accessibility, inter-individual variability, and concerns over specificity and generalizability. The lack of objective measures highlights the complex biopsychosocial nature of pain, involving interactions between sensory input, emotion, cognition, and context, which has shifted research focus toward biological correlates that reflect underlying pathophysiology rather than subjective symptoms alone. Chronic pain is increasingly seen as a state of persistent inflammatory and metabolic dysregulation, with evidence showing alterations in inflammatory biomarkers such as interleukin-6, tumor necrosis factor-α, and C-reactive protein across conditions like low back pain and fibromyalgia, providing quantifiable indices of immune activation even when structural pathology is absent or poorly correlated with symptoms. Metabolomic studies have also identified distinct metabolic signatures in chronic pain, including changes in energy metabolism, oxidative stress, and micronutrient balance. Despite these advances, no single biomarker has yet been validated for routine clinical use, leading research toward multimodal biosignatures that integrate inflammatory, metabolic, neurobiological, and psychosocial data, with large-scale programs like the NIH Acute to Chronic Pain Signatures initiative aiming to develop predictive, mechanism-informed biomarkers to improve diagnosis, prognostication, and personalized treatment strategies.[15]

Therefore, the present study aimed to experimentally evaluate the relationship between inflammatory and metabolic biomarkers and chronic pain severity in patients with pulmonary diseases, with the goal of identifying objective, rapid, and sensitive indicators for clinical pain assessment.

MATERIAL AND METHODS

Study Design and Setting

This experimental case-control study was conducted at Imran Idrees Teaching Hospital, Pakistan Institute of Medical Sciences, Islamabad, from January 2024 to September 2024.

Ethical Approval

Ethical approval was obtained from the Institutional Research Ethics Committee (Ref No: ERC/PIMS/2024-017), in accordance with the Declaration of Helsinki.

Sample

A total of 180 participants were enrolled, including 120 diagnosed pulmonary disease patients experiencing chronic pain and 60 age- and sex-matched healthy controls.

Inclusion Criteria

Patients aged 30–70 years with clinically diagnosed chronic pulmonary disease and persistent pain lasting ≥3 months were included.

Exclusion Criteria

Patients with malignancy, autoimmune disease, acute infection, recent surgery, or long-term corticosteroid therapy were excluded.

Pain Assessment

Pain intensity was assessed using the Visual Analog Scale (VAS), ranging from 0 (no pain) to 10 (severe pain).

Biomarker Assessment

Venous blood samples were collected after overnight fasting. Serum CRP was measured using immunoturbidimetric assay. IL-6 and TNF-α were quantified by ELISA. Fasting glucose and insulin levels were measured enzymatically, and insulin resistance was calculated using HOMA-IR.

Statistical Analysis

Data were analyzed using SPSS version 26.0. Results were expressed as mean ± SD. Independent t-tests and Pearson correlation analyses were performed. A p-value <0.05 was considered statistically significant.

RESULTS

Table 1: Demographic and Clinical Characteristics

Parameter	Patients (n=120)	Controls (n=60)	p-value
Age (years)	55.3 ± 8.6	54.1 ± 7.9	0.42
Male (%)	62.5	60.0	0.71
VAS Score	6.8 ± 1.2	1.4 ± 0.6	<0.001

Patients demonstrated significantly higher pain scores compared to controls.

Table 2: Inflammatory Biomarker Levels

Biomarker	Patients	Controls	p-value
CRP (mg/L)	6.42 ± 1.18	1.92 ± 0.54	<0.001
IL-6 (pg/mL)	14.6 ± 3.9	4.1 ± 1.2	<0.001
TNF-α (pg/mL)	18.3 ± 4.7	7.2 ± 2.0	<0.001

All inflammatory markers were markedly elevated in patients.

Table 3: Metabolic Biomarkers and Correlation with Pain

Parameter	Patients	Controls	Correlation with VAS (r)
Fasting Glucose (mg/dL)	112 ± 18	92 ± 11	0.61
Insulin (μIU/mL)	15.8 ± 4.2	7.9 ± 2.1	0.68
HOMA-IR	3.12 ± 0.86	1.41 ± 0.39	0.74

Table 1: Demographic and Clinical Characteristics Parameter Patients (n=120) Controls (n=60) p-value Age (years) 55.3 ± 8.6 54.1 ± 7.9 0.42 Male (%) 62.5 60.0 0.71 VAS Score 6.8 ± 1.2 1.4 ± 0.6 <0.001 Patients demonstrated significantly higher pain scores compared to controls. Table 2: Inflammatory Biomarker Levels Biomarker Patients Controls p-value CRP (mg/L) 6.42 ± 1.18 1.92 ± 0.54 <0.001 IL-6 (pg/mL) 14.6 ± 3.9 4.1 ± 1.2 <0.001 TNF-α (pg/mL) 18.3 ± 4.7 7.2 ± 2.0 <0.001 All inflammatory markers were markedly elevated in patients. Table 3: Metabolic Biomarkers and Correlation with Pain Parameter Patients Controls Correlation with VAS (r) Fasting Glucose (mg/dL) 112 ± 18 92 ± 11 0.61 Insulin (μIU/mL) 15.8 ± 4.2 7.9 ± 2.1 0.68 HOMA-IR 3.12 ± 0.86 1.41 ± 0.39 0.74 Metabolic dysregulation showed strong positive correlation with pain severity.

The results are summarized in three tables describing demographic characteristics, inflammatory biomarkers, and metabolic parameters in patients and controls.

A total of 120 patients and 60 control participants were included in the analysis. As shown in Table 1, there were no statistically significant differences between the two groups with respect to age or sex distribution. The mean age of patients was 55.3 ± 8.6 years, compared with 54.1 ± 7.9 years in controls. Male participants constituted 62.5% of the patient group and 60.0% of the control group. In contrast, pain intensity measured using the visual analog scale was significantly higher in patients than in controls, with mean scores of 6.8 ± 1.2 and 1.4 ± 0.6, respectively.

Inflammatory biomarker levels are presented in Table 2. Patients exhibited markedly elevated concentrations of all measured inflammatory markers compared with controls. Mean C-reactive protein levels were 6.42 ± 1.18 mg/L in patients and 1.92 ± 0.54 mg/L in controls. Interleukin-6 levels were 14.6 ± 3.9 pg/mL in patients, compared with 4.1 ± 1.2 pg/mL in controls, while tumor necrosis factor-alpha levels were 18.3 ± 4.7 pg/mL and 7.2 ± 2.0 pg/mL, respectively. All differences were statistically significant.

Table 3 summarizes metabolic parameters and their relationship with pain severity. Patients demonstrated higher fasting glucose, insulin levels, and HOMA-IR values compared with controls, indicating greater metabolic dysregulation. Fasting glucose levels averaged 112 ± 18 mg/dL in patients and 92 ± 11 mg/dL in controls, while insulin levels were 15.8 ± 4.2 μIU/mL and 7.9 ± 2.1 μIU/mL, respectively. The mean HOMA-IR value was 3.12 ± 0.86 in patients compared with 1.41 ± 0.39 in controls. All metabolic parameters showed strong positive correlations with pain intensity, with correlation coefficients ranging from 0.61 to 0.74, indicating that greater metabolic impairment was associated with higher pain severity

Metabolic dysregulation showed strong positive correlation with pain severity.

DISCUSSION

The present experimental study demonstrates that patients with chronic pulmonary diseases experiencing persistent pain exhibit significantly elevated inflammatory and metabolic biomarkers compared to healthy controls. These findings support the hypothesis that chronic pain in pulmonary disease is closely linked to systemic biological alterations rather than being purely subjective.

Elevated CRP, IL-6, and TNF-α levels observed in this study align with previous reports identifying inflammatory cytokines as mediators of nociceptive sensitization and pain chronicity [9,10]. These cytokines are known to amplify peripheral and central pain signaling, particularly in chronic inflammatory conditions [11].

The observed metabolic abnormalities, including increased fasting glucose, insulin, and HOMA-IR, further highlight the interplay between metabolic dysfunction and pain perception. Insulin resistance has been shown to exacerbate inflammatory signaling and neural excitability, thereby intensifying chronic pain experiences [12,13].

Compared with earlier studies that examined either inflammatory or metabolic markers in isolation, the novelty of this study lies in the integrated evaluation of both biomarker categories within a pulmonary disease population [14]. The strong correlations between biomarker levels and VAS scores suggest their potential utility as objective, quantifiable pain indicators.

These findings may facilitate rapid, sensitive, and reproducible pain assessment in clinical settings, overcoming limitations of subjective reporting. However, longitudinal studies are required to validate causality and assess biomarker responsiveness to therapeutic interventions.

CONCLUSION

This study demonstrates that inflammatory and metabolic biomarkers serve as novel, objective, and sensitive indicators of chronic pain in patients with pulmonary diseases. Their rapid measurability and strong correlation with pain severity highlight their potential clinical utility for early detection, monitoring, and personalized pain management strategies.

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ETHICS STATEMENT

This study was approved by the Institutional Research Ethics Committee of Pakistan Institute of Medical Sciences (ERC/PIMS/2024-017).

INFORMED CONSENT

Written informed consent was obtained from all participants prior to enrollment.

COMPETING INTERESTS

The authors declare no competing interests.

FINANCIAL DISCLOSURE

This research received no external funding.

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