

Association of Clinical and Lifestyle Factors with TNF- α Gene Expression in Patients with Chronic Low Back Pain: A Cross-Sectional Study from South Sulawesi

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ABSTRACT

Background and Objective: Chronic low back pain is a leading cause of disability worldwide and is associated with complex interactions among inflammatory, genetic, and lifestyle-related factors. Tumor necrosis factor-alpha (TNF- α) plays a pivotal role in neuroinflammation and intervertebral disc degeneration, yet the influence of clinical risk factors on its gene expression remains unclear. This study investigated the association between demographic and lifestyle-related risk factors and TNF- α gene expression in patients with chronic low back pain.

Materials and Methods: A cross-sectional study was conducted involving 41 patients with chronic low back pain. Nineteen healthy individuals were included as a reference group for calibrating relative TNF- α gene expression. Demographic characteristics, smoking status, body mass index (BMI), physical activity, and pain intensity were assessed in patients with chronic low back pain. Relative TNF- α gene expression in peripheral blood was quantified using reverse transcription quantitative polymerase chain reaction and analyzed using nonparametric statistical tests.

Results: The mean age of the 41 patients was 48.90 ± 14.27 years, and most patients reported high physical activity levels (48.8%) and had normal BMI (46.3%). Median relative TNF- α gene expression was 1.37 (range, 0.09–20.76). Furthermore, TNF- α gene expression showed no significant association with age, sex, smoking status, BMI, physical activity, or pain intensity (all $p > 0.05$).

Conclusions: TNF- α gene expression was not significantly associated with demographic or lifestyle-related risk factors in chronic low back pain, suggesting that inflammatory gene regulation is influenced by multifactorial biological mechanisms beyond conventional clinical characteristics.

Keywords: Risk Factors; Chronic Low Back Pain; Gene Expression; Tumor Necrosis Factor-alpha; Cross-Sectional Studies; Reverse Transcriptase Polymerase Chain Reaction

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INTRODUCTION

Chronic low back pain (CLBP) is defined as pain localized between the lower costal margin and the inferior gluteal folds, with or without radiating leg pain, persisting for at least 12 weeks [1]. CLBP is the leading cause of years lived with disability worldwide and imposes a substantial socioeconomic burden across all age groups [2]. More than 85% of patients present with non-specific CLBP without an identifiable structural lesion, highlighting the complexity of its underlying pathophysiology [3]. Although most episodes of acute low back pain resolve

spontaneously, approximately one-fifth progress to chronic pain, suggesting that biological susceptibility contributes to pain persistence beyond mechanical injury alone [4]. Increasing evidence indicates that interactions among genetic predisposition, environmental exposure, and lifestyle-related factors are involved in the transition from acute to chronic low back pain [5].

Neuroinflammation has emerged as a central mechanism in the development and maintenance of CLBP, particularly in patients with intervertebral disc degeneration [6]. Among inflammatory mediators, tumor necrosis factor-

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alpha (TNF- α) is one of the principal cytokines driving extracellular matrix degradation, nociceptor sensitization, and persistent inflammatory signaling within degenerated discs [7]. TNF- α also stimulates the production of neurotrophic factors, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), promoting aberrant nerve ingrowth and central sensitization that sustain chronic pain [8]. Recent genomic studies further suggest that altered expression of pain-related and inflammatory genes contributes to individual variability in disease susceptibility and clinical severity, supporting the use of gene expression profiling as a potential biomarker for precision medicine in CLBP [9].

Several modifiable risk factors, including obesity, smoking, physical inactivity, sleep disturbance, and psychological disorders, have consistently been associated with an increased risk of CLBP [10]. Obesity promotes chronic low-grade inflammation through adipokine dysregulation and oxidative stress, whereas cigarette smoking enhances TNF- α production and amplifies inflammatory signaling pathways [11]. Likewise, chronic psychological stress and depression activate the hypothalamic-pituitary-adrenal axis, leading to glucocorticoid resistance and sustained expression of pro-inflammatory genes, while regular physical activity exerts anti-inflammatory effects by modulating cytokine signaling [12,13]. Despite these findings, previous studies have primarily evaluated epidemiological associations or circulating inflammatory proteins, and few have directly investigated the contribution of clinical risk factors to TNF- α gene expression in patients with CLBP [14]. Therefore, this cross-sectional study aimed to evaluate the contribution of demographic and lifestyle-related risk factors to TNF- α gene expression among patients with chronic low back pain, providing molecular evidence that may facilitate risk stratification and support personalized preventive and therapeutic strategies [15].

MATERIALS AND METHODS

Study Design and Setting

This analytical observational study employed a cross-sectional design to investigate the association of clinical and lifestyle-related risk factors to TNF- α gene expression in patients with chronic low back pain. Participant recruitment was conducted from January 2026 until July 2026 at the Neurology Outpatient Clinic and Neurology Inpatient Department of Dr. Wahidin Sudirohusodo Hospital and affiliated teaching hospitals in Makassar, Indonesia. Molecular analyses, including total RNA extraction, complementary DNA (cDNA) synthesis, and quantitative gene expression analysis, were performed at the Hasanuddin University Teaching Hospital Molecular Biology Laboratory.

Study Population

The study population consisted of adult patients attending neurology services at participating hospitals who were diagnosed with chronic low back pain according to clinical history and neurological examination, defined as pain

persisting for at least 12 weeks with or without radicular symptoms. Participants were required to be at least 18 years of age and to provide written informed consent before enrollment. In addition, 19 healthy individuals were included as a reference group solely for the determination of the calibrator ΔC_t used in relative TNF- α gene expression analysis. The association between clinical and lifestyle-related factors and TNF- α gene expression was evaluated exclusively among the 41 patients with chronic low back pain.

Eligibility Criteria

Patients were excluded if they had acute infection, malignancy, vertebral fracture, previous lumbar spine surgery, active systemic inflammatory disease, pregnancy or lactation, epidural steroid injection or spinal surgery within the preceding three months, severe spinal deformity, unstable major systemic disease, or current systemic corticosteroid or immunomodulatory therapy. Samples with quantitative PCR cycle threshold (C_t) values greater than 40 were excluded from the final molecular analysis because they were considered insufficient for reliable quantification.

Sample Size and Sampling Technique

Participants were recruited consecutively until the minimum sample size was achieved. The required sample size was calculated using the formula for comparing two independent proportions with a significance level of 5% and statistical power of 80%, assuming an expected exposure proportion of 0.32 among cases and 0.68 among controls. The minimum sample size was estimated to be 30 participants. Healthy controls were recruited using the same eligibility criteria except for the absence of chronic low back pain.

Clinical Data Collection

Eligible participants underwent standardized interviews and neurological examinations performed by trained neurologists. Demographic characteristics, including age and sex, were obtained from medical records. BMI was calculated as body weight divided by the square of height (kg/m^2). Smoking status was assessed using the Brinkman Index and categorized according to cumulative tobacco exposure. Physical activity was evaluated using the International Physical Activity Questionnaire (IPAQ) and classified into low, moderate, or high activity levels. Clinical and laboratory data were recorded using anonymized study identification codes to maintain participant confidentiality.

Blood Collection and RNA Isolation

Peripheral venous blood (2–3 mL) was collected aseptically into EDTA-containing tubes and stored at 2–8°C until processing. Total RNA was extracted from whole blood using a commercial RNA extraction kit according to the manufacturer's instructions. RNA concentration and purity were assessed using a NanoDrop spectrophotometer, and only samples demonstrating acceptable purity (A_{260}/A_{280} ratio >1.0) proceeded to reverse transcription.

Reverse Transcription and Quantitative PCR

Complementary DNA was synthesized using the ReverTra Ace™ qPCR RT Master Mix with gDNA Remover (TOYOBO FSQ-301, Osaka, Japan). Relative TNF- α gene expression was quantified by real-time quantitative polymerase chain reaction using GAPDH as the endogenous reference gene. Amplification reactions were performed on a Bio-Rad CFX Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA, USA) with

a total reaction volume of 10 μ L containing 2 $\times$ SYBR Green Master Mix, forward and reverse primers (See Table 1), cDNA template, and nuclease-free water.

PCR cycling conditions consisted of an initial denaturation at 95°C for 15 min, followed by 50 amplification cycles of denaturation at 95°C for 15 s and annealing at 62.6°C for 30 s. A melting-curve analysis ranging from 65°C to 95°C was performed to verify amplification specificity. All reactions were analyzed in duplicate.

Table 1. Primer Sequences Used for Quantification of TNF- α Gene Expression by RT-qPCR

Gene	Forward Primer (5'–3')	Reverse Primer (5'–3')
TNF- α	TTCCTGATCGTGGCAGGC	GCTGATTAGAGAGTCCCTG
GAPDH	TCGTGGAAGGACTCATGACC	ATGATGTTCTGGAGAGCCCC

Gene Expression Analysis

Relative TNF- α gene expression was determined using the comparative Ct ($2^{-\Delta\Delta Ct}$) method, with GAPDH as the endogenous reference gene. For each participant, ΔCt was calculated as the difference between the Ct value of TNF- α and the Ct value of GAPDH. The mean ΔCt of 19 healthy individuals was used as the calibrator (mean ΔCt = 6.38). $\Delta\Delta Ct$ was calculated by subtracting the calibrator ΔCt from the ΔCt of each patient with chronic low back pain. Relative TNF- α expression was subsequently expressed as fold change using the $2^{-\Delta\Delta Ct}$ method. The 19 healthy individuals served solely as the reference group for relative gene expression normalization, whereas analyses of the associations between clinical and lifestyle factors and TNF- α expression were performed among the 41 patients with chronic low back pain.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean $\pm$ standard deviation or median (minimum–maximum) according to data distribution, whereas categorical variables were expressed as frequencies and percentages. Data normality was assessed using the Shapiro–Wilk test. Because relative TNF- α gene expression was not normally distributed, its association with continuous variables (age, BMI, and pain intensity) was assessed using Spearman's rank correlation test. Comparisons of TNF- α expression between two categorical groups were performed using the Mann–Whitney U test, whereas comparisons among more than two groups were performed using the Kruskal–Wallis test. Statistical significance was defined as a two-tailed p value <0.05 .

Ethical Considerations

The study protocol was approved by the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia (Approval No. 261A/UN4.6.4.5.31/PP36/2026). Written informed consent was obtained from all participants prior to enrollment. All procedures were conducted in accordance with the principles of the Declaration of Helsinki, and participant confidentiality was maintained throughout the study.

RESULTS

Participant Characteristics

A total of 41 patients with chronic low back pain were enrolled in this cross-sectional study. The demographic and clinical characteristics of the study population are summarized in Table 2.

The mean age of patients was 48.90 ± 14.27 years (range, 21–70 years), with most patients aged 45–64 years (53.7%). Sex distribution was relatively balanced, with females comprising 51.2% of participants. Most patients were non-smokers (75.6%), had a normal BMI (mean 23.75 ± 4.70 kg/m²; 46.3% within the normal range), and reported high physical activity levels (48.8%). Hypertension was present in 24.4% of patients, whereas diabetes mellitus and dyslipidemia were observed in 4.9% and 12.2% of patients, respectively.

The median pain intensity was 7 (range, 5–9) on the Numerical Pain Rating Scale (NPRS) and 7 (range, 5–10) on the Visual Analog Scale (VAS). Median relative TNF- α gene expression among patients was 1.37 (range, 0.09–20.76).

Table 2. Baseline Characteristics of the Study Population (n = 41)

Variable	n	%
Age (years), mean $\pm$ SD	48.90 ± 14.27	–
18–29	4	9.8
30–44	12	29.3
45–64	22	53.7
≥ 65	3	7.3
Sex		
Male	20	48.8
Female	21	51.2

Smoking status (Brinkman Index)		
Non-smoker	31	75.6
Light smoker	6	14.6
Moderate smoker	3	7.3
Heavy smoker	1	2.4
BMI (kg/m ²), mean $\pm$ SD	23.75 $\pm$ 4.70	–
Underweight	6	14.6
Normal weight	19	46.3
Overweight	16	39.0
Physical activity (IPAQ)		
Low	11	26.8
Moderate	10	24.4
High	20	48.8
History of hypertension		
No	31	75.6
Yes	10	24.4
History of diabetes mellitus		
No	39	95.1
Yes	2	4.9
History of dyslipidemia		
No	36	87.8
Yes	5	12.2
Pain intensity, median (min–max)		
NPRS	7 (5–9)	–
VAS	7 (5–10)	–
Relative TNF-α gene expression, median (min–max)	1.37 (0.09–20.76)	

Data are presented as mean $\pm$ standard deviation, median (minimum–maximum), or n (%), as appropriate. Abbreviations: SD, standard deviation; IPAQ, International Physical Activity Questionnaire; NPRS, Numerical Pain Rating Scale; VAS, Visual Analog Scale; TNF- α , tumor necrosis factor-alpha.

Association Between Clinical Risk Factors and TNF- α Gene Expression

The associations between clinical risk factors and relative TNF- α gene expression are presented in Table 3. No significant difference in TNF- α expression was observed according to sex ($p = 0.449$) or diabetes status ($p = 0.904$).

Likewise, TNF- α expression did not differ significantly according to smoking status ($p = 0.346$) or physical activity level ($p = 0.572$). TNF- α expression did not differ significantly across smoking-status categories ($p=0.346$). The heavy-smoking category comprised only one participant, limiting interpretation of this subgroup. TNF- α expression also did not differ significantly across age groups ($p = 0.103$), despite a numerically higher median observed among patients aged 18–29 years (6.17), a subgroup comprising only 4 patients. Relative TNF- α expression did not differ significantly across BMI categories ($p=0.351$).

Table 3. Association Between Clinical and Lifestyle Factors and Relative TNF- α Gene Expression ($n = 41$)

Variable	Relative TNF- α Expression, Median (Min–Max)	p value
Age group (years)		0.103 ^b
18–29	6.17 (1.37–11.39)	
30–44	1.76 (0.48–6.50)	
45–64	1.01 (0.09–20.76)	
≥ 65	1.43 (0.86–13.27)	
Sex		0.449 ^a
Male	1.32 (0.20–20.76)	
Female	1.37 (0.09–6.50)	
Smoking status		0.346 ^b
Non-smoker	1.19 (0.09–20.76)	
Light smoker	1.58 (0.48–11.39)	
Moderate smoker	1.44 (1.19–2.58)	
Heavy smoker	13.27 ($n = 1$)	

Physical activity		0.572 ^b
Low	1.44 (0.20–20.76)	
Moderate	1.51 (0.24–13.27)	
High	1.19 (0.09–4.20)	
BMI		0.351 ^b
Underweight	0,87 (0,19-2,62)	
Normal weight	1,83 (0,09-20,76)	
Overweight	1,32 (0,20-11,39)	

^a Mann–Whitney U test; ^b Kruskal–Wallis test.

Correlation Between Pain Intensity and TNF- α Gene Expression

Spearman correlation analysis demonstrated no significant correlation between relative TNF- α expression and pain intensity measured using the Numerical Pain Rating Scale ($r = -0.069$; $p = 0.668$) or the Visual Analog Scale ($r = -$

0.008 ; $p = 0.962$) (Table 4). Although both correlation coefficients were negative, their magnitudes were weak, indicating that increased pain intensity was not accompanied by a corresponding increase in peripheral TNF- α gene expression in the study population.

Table 4. Correlation Between Pain Intensity and Relative TNF- α Gene Expression

Variable	Spearman's r	p value
Numerical Pain Rating Scale (NPRS)	-0.069	0.668
Visual Analog Scale (VAS)	-0.008	0.962

Correlation analysis was performed using Spearman's rank correlation test.

DISCUSSION

This cross-sectional study evaluated the contribution of demographic and lifestyle-related risk factors to TNF- α gene expression among 41 patients with chronic low back pain. Although relative TNF- α expression varied considerably across individuals (median 1.37; range, 0.09–20.76), none of the evaluated risk factors, including age, sex, smoking status, BMI, physical activity, or pain intensity, demonstrated a statistically significant association with TNF- α gene expression. These findings suggest that, within this cohort, variation in peripheral TNF- α gene expression was not adequately captured by the individual clinical and lifestyle characteristics evaluated in this study. This observation is consistent with the systematic review by Morris et al. (2020), which concluded that although TNF- α is implicated in chronic low back pain, the available evidence remains inconsistent and is substantially influenced by differences in study populations, disease stages, and analytical methodologies [16].

TNF- α gene expression did not differ significantly across age groups ($p=0.103$). Although the youngest age group showed a numerically higher median TNF- α expression, this subgroup consisted of only four participants, limiting the reliability of this observation. These findings are in line with Lisiewski et al. (2026), who reported that age was not significantly correlated with immune-related gene expression in patients with low back pain [17]. One possible explanation is that inflammatory gene expression reflects ongoing pathological activity rather than chronological aging. Degenerative changes, disc herniation severity, mechanical loading, and local inflammatory responses may exert a greater influence on TNF- α transcription than age itself. Furthermore, reduced expression of TNF receptor I during advanced disc

degeneration may attenuate the biological effects of TNF- α despite preserved cytokine expression, as previously demonstrated by Le Maitre et al. (2007) [18]. Similarly, sex was not associated with differential TNF- α expression. Although estrogen and testosterone modulate inflammatory signaling through NF- κ B-dependent pathways, the intense inflammatory microenvironment accompanying chronic disc degeneration may outweigh physiological sex-related differences. These findings agree with Teodorczyk-Injeyan et al. (2019), who demonstrated that variations in TNF- α levels were more closely related to disease mechanisms than demographic characteristics [19].

Smoking status, BMI, and physical activity also showed no significant association with TNF- α expression. Cigarette smoking has been shown to induce oxidative stress and activate NF- κ B signaling, thereby increasing TNF- α transcription in disc cells, whereas obesity promotes chronic low-grade inflammation through adipose tissue macrophage activation, and moderate physical activity suppresses inflammatory cytokine production via myokine-mediated mechanisms [20–22]. Nevertheless, the absence of significant associations in the present study may reflect exposure misclassification, insufficient quantification of cumulative smoking burden, heterogeneity in obesity-related inflammatory phenotypes, and the limited accuracy of self-reported physical activity assessed using the International Physical Activity Questionnaire. These findings are consistent with Jang et al. (2020), who suggested that obesity-related alterations in peripheral blood gene expression do not necessarily translate into changes in individual inflammatory genes, and with Moldoveanu et al. (2000), who reported that circulating TNF- α responses following physical activity were not accompanied by corresponding changes in TNF- α mRNA expression [23,24]. Likewise, pain intensity measured using the Numerical Pain Rating Scale and

Visual Analog Scale was not correlated with TNF- α expression, supporting previous evidence that subjective pain perception is strongly influenced by psychological factors and central sensitization rather than peripheral inflammatory biomarkers alone [25].

Several limitations should be considered when interpreting these findings. First, the cross-sectional design captures TNF- α expression and clinical risk factors at a single time point, precluding causal or temporal inferences and limiting the ability to determine whether observed associations reflect cause, consequence, or a shared underlying process. Second, Although 19 healthy individuals were included as a reference group for relative gene expression normalization, they were not included as a comparative clinical cohort. Therefore, the present study was not designed or powered to formally compare TNF- α gene expression between patients with chronic low back pain and healthy individuals. Third, chronic low back pain comprises heterogeneous nociceptive, neuropathic, and nociplastic phenotypes, and peripheral TNF- α expression may inadequately capture mechanisms predominantly driven by central sensitization. Fourth, the relatively small sample size, particularly within comorbidity and smoking subgroups, may have limited statistical power to detect modest associations. Finally, interindividual genetic variability, including promoter polymorphisms affecting TNF- α transcription, and residual confounding related to medication use, sleep quality, and psychosocial status were not evaluated and could not be completely excluded. Collectively, these findings indicate that TNF- α gene expression alone is unlikely to serve as a robust molecular marker of individual risk factors in chronic low back pain, highlighting the need for future studies integrating genomic, clinical, and psychosocial determinants to better characterize the biological mechanisms underlying pain chronification.

CONCLUSIONS

This cross-sectional study of 41 patients with chronic low back pain demonstrated that demographic and lifestyle-related risk factors, including age, sex, smoking status, BMI, physical activity, and pain intensity, were not significantly associated with TNF- α gene expression. These findings suggest that peripheral TNF- α expression is unlikely to be explained by individual clinical risk factors alone and instead reflects the complex and multifactorial biological mechanisms underlying chronic low back pain. Future studies incorporating larger sample sizes, a comparison group, longitudinal designs, comprehensive molecular profiling, and adjustment for potential confounding factors are warranted to better elucidate the determinants of inflammatory gene expression and identify clinically relevant biomarkers for precision medicine.

DECLARATIONS

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Author Contributions

PP: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft.

ADW: Conceptualization, Methodology, Supervision, Writing – Review & Editing.

NH: Investigation, Validation, Resources, Writing – Review & Editing.

MNM: Methodology, Investigation, Validation, Resources, Supervision.

SA: Investigation, Data Curation, Validation, Writing – Review & Editing.

YG: Conceptualization, Methodology, Supervision, Project Administration, Writing – Review & Editing.

Informed Consent Statement

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

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no competing interests.

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