# MACROPHAGE MIGRATION INHIBITORY FACTOR EXPRESSION IN LUNG DISEASES: AN EXPLORATORY GENE EXPRESSION PROFILING STUDY

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Macrophage Migration Inhibitory Factor (MIF) is a key inflammatory cytokine implicated in immune regulation and tumour biology. Its role in lung disease, particularly in relation to tumour differentiation and clinical risk, remains incompletely understood. This study aimed to evaluate the expression pattern of MIF in lung disease using gene expression profiling, assess its variation across histological grades, and determine its association with clinical risk. A secondary data-based exploratory analysis was conducted using microarray gene expression data from 442 lung tissue samples obtained from a publicly available dataset. MIF expression was extracted using probe ID 200799_at from the Affymetrix Human Genome U133A platform. Samples stratified based on histological differentiation into well, moderate, and poorly differentiated groups. Statistical analyses included descriptive statistics, Welch's t-test, Pearson correlation, and linear regression. MIF expression demonstrated a significant increase with decreasing tumour differentiation, with the highest levels observed in poorly differentiated tumours (11.05±0.68). Independent t-tests confirmed significant differences between all histological groups ($p<0.05$). However, correlation analysis revealed a weak and non-significant association with clinical risk ($r=0.06$, $p=0.20$) and regression analysis indicated minimal predictive power ($R^2=0.003$). MIF expression is significantly associated with tumour differentiation in lung disease but lacks predictive value for clinical risk. These findings suggest that MIF serves as a marker of tumour biology rather than a standalone prognostic biomarker.

**Keywords:** macrophage migration inhibitory factor, lung cancer, gene expression, tumour differentiation

**Introduction.** Lung diseases, such as lung cancer and other adverse chronic pulmonary diseases are a major global health burden, where in the underlying molecular and inflammatory mechanisms that cause the disease complicate the progression of the disease. These processes involves some of the main molecular mediators such as MIF, a versatile cytokine that reported to mediate immune reactions, inflammation and cellular signaling pathway. It evidenced in previous research findings that MIF is important in tumour biology and inflammatory settings, with the association found between the severity and progression of diseases in many types of cancer [1]. Transcriptomic and proteomic studies have also shown that immune-related pathways, such as MIF signaling play a role in pathology of lung tissue and fibrosis [2]. The use of biomarker-based methods in pulmonary diseases used to gain insight into the heterogeneity of the diseases and predict the clinical outcome with a focus on the role of immune mediators in respiratory diseases [3]. In addition, new transcriptomics have given insights on tissue-specific responses and susceptibility trajectories in diseases related to the lungs, which signify the importance of gene expression profiling in dissecting disease pathogenesis [4]. The effect of MIF on cellular homeostasis and barrier maintenance investigated in times of stress leading to the idea that MIF is involved in inflammatory regulation and tissue remodelling [5]. Clinically, MIF has been gaining more and more importance as an essential mediator of infections and inflammatory diseases and its uncontrolled activity leads to pathological processes [6]. MIF identified in respiratory diseases like asthma and chronic obstructive pulmonary disease (COPD) as an inflammatory mediator and a disease progression factor, which suggests that MIF may be a treatment target [7]. Moreover, its contribution to the wider range of immune pathophysiological processes in systemic diseases highlights its importance in regulating the immune system and the dynamics of diseases [8]. Taken together, these results indicate the need to study MIF expression in the lung disease settings in the context of the advanced transcriptomic methods.

Although an increasing number of studies propose the role of MIF in the process of inflammation and immune-related mechanisms, there are still a number of gaps in knowledge about the specific role of MIF in lung disease. Although

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research previously conducted into the molecular interactions of MIF with chemokine receptors and the inflammatory pathway [9] there has been a lack of research on the expression patterns of MIF in the various degrees of tumour differentiation in lung disease. In the same way, even though MIF studied in the systemic inflammatory conditions and post-disease recovery profiles [10], its particular role in the tumour heterogeneity and differentiation in lung cancer not comprehensively investigated. The development of transcriptomic and multi-omics methods has given a better understanding of how the genes regulated and the mechanisms of diseases, but the combination of these methods in assessing the MIF expression in pulmonary disease remains scarce [11]. Past transcriptomic research has discovered MIF-related gene networks in several diseases [12], but it has not been applied to lung disease and especially clinical stratification. In addition, they found to differ in MIF expression among physiological and clinical conditions [13], but their role in predicting disease severity or clinical risk in lung disease has not been explicitly determined. Such gaps indicate that a focused study to determine the expression dynamics of MIF in lung disease is necessary and especially in connection to tumour differentiation and clinical outcomes based on gene expression profiling.

Since the role of MIF in inflammatory and immune-mediated processes is complicated, the expression patterns of this protein in lung disease need study that is more detailed. Transcriptomic studies have shown that MIF-related gene networks are similar significantly altered in different pathological conditions and therefore is involved in disease progression in a context-dependent manner [14]. Moreover, the changes of MIF levels among physiological conditions and early-life indicate its dynamical regulation capability in immune responses [15].

Gene expression profiling is one of these potent technologies that have facilitated the study of the disease pathophysiology, including the determination of key biomarkers and pathways related to disease progression [16]. The clinical importance of inflammatory cytokines, such as MIF in the context of lung disease linked to change in the lung functioning and chronic disease conditions highlighting its clinical significance [17]. Thus, **the aim of the study** is to use the data of the microarray-based gene expression to examine the expression pattern of MIF in lung disease. The study aims to offer understanding of the effect of MIF on tumour differentiation and its possible clinical use by integrating clinical stratification and transcriptomic analysis.

**Material and Methods.** *Study Design and Data Source.* The study has used an exploratory research design using secondary data because it aims at establishing the expression pattern of Macrophage Migration Inhibitory Factor (MIF) in lung disease. There was the use of publicly available gene expression data and linked clinical data. The data was retrieved in the Kaggle repository where microarray data of patients with lung cancer is curated [18]. The data consisted of 442 lung tissues, prepared through Affymetrix Human Genome U133A microarray platform, which allowed performing the transcriptomic profiling of the genome on a large scale.

*Clinical Data and Gene Expression Processing with Group Stratification.* The data consisted of pre-processed and normalized values of gene expressions and clinical covariates of each sample. Affymetrix probe ID 200799 at which the gene Macrophage Migration Inhibitory Factor was represented was used to extract MIF expression that was then retained in its normalized form to be analysed. The samples stratified on clinical variables by histological differentiation (Hgrade) into well-differentiated, moderately differentiated and poorly differentiated samples to compare MIF expression levels in samples with different levels of tumour differentiation and examine its relationship with the severity of the disease.

*Data Integration.* To provide proper correspondence between transcriptomic variables and clinical variables, the data of gene expression combined with the clinical covariate data based on unique sample identifiers. The analysis took into consideration only samples that had complete data on gene expression and histological grading.

*Statistical Analysis.* To describe the level of MIF expression in the study population and histological subgroups, descriptive statistics such as mean, standard deviation, median, minimum and maximum values calculated. Independent t-test, Welch independent t-test was used to compare differences in expressions in groups and Pearson correlation analysis was done to measure the relationship between MIF expression and clinical risk. In addition, simple linear regression model was used to assess predictive potential of MIF expression with regression coefficients (β), standard

errors, t-values, p-values, and model fit indices ($R^2$ and adjusted $R^2$) being reported. The p-value of less than 0.05 was taken to be statistically significant.

**Results.** *Cohort Composition and Clinical Landscape of the Study Population.* The dataset of the study was the 442 samples of lung tissue, which studied with the help of the Affymetrix Human Genome U133A microarray platform. Histological differentiation and clinical stratification identified moderately differentiated tumours as the prevalent ones, with poorly differentiated and well-differentiated ones after that. Precisely, moderate differentiation contributed 47.3% (n=209), poorly differentiated tumours were 37.6% (n=166) and 13.6% (n=60), respectively, of the cohort, which provided a heterogeneous clinical distribution to be examined by stratified transcriptomic analysis (Tab. 1).

**Table 1.**

Clinical Distribution of Study Cohort

| Histological Grade | n | (%) |
|---|---|---|
| Well Differentiated | 60 | 13.60 |
| Moderate Differentiation | 209 | 47.30 |
| Poorly Differentiated | 166 | 37.60 |
| **Total** | **442** | **100** |

The distribution of histological differentiation categories showed a predominance of moderately differentiated tumours, while poorly differentiated tumours also represented a substantial proportion, indicating that the cohort was skewed toward more advanced pathological conditions (Fig. 1). Well-differentiated tumours accounted for a smaller percentage, suggesting limited representation of early-stage differentiation. This distribution supports the suitability of the dataset for comparing gene expression across different levels of tumour severity.

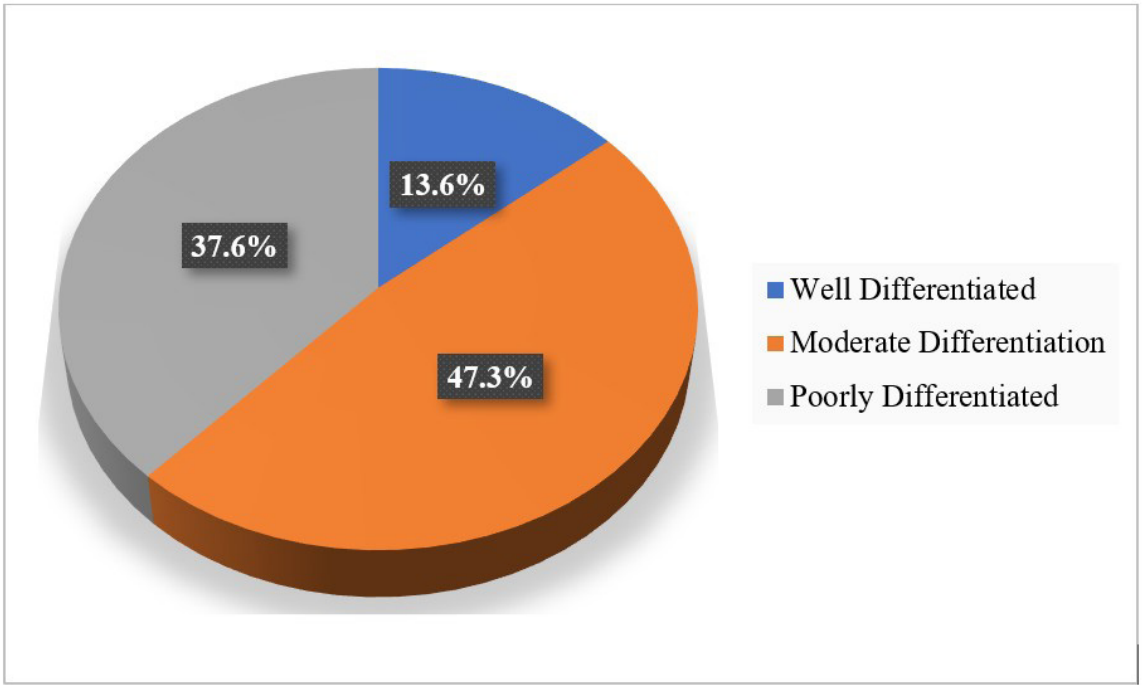


**Fig. 1. Distribution of Histological Grades in the Study Cohort**

*Stratified Expression Patterns across Histopathological Grades.* The presence of Macrophage Migration Inhibitory Factor (MIF) showed an increasing trend by the grade of histology. The lowest mean expression values were in well differentiated tumours (10.58±0.60),

moderately differentiated tumours (10.78±0.71) and in poorly differentiated tumours (11.05±0.68). The median values also showed a steady increasing pattern (10.62, 10.83 and 11.09 respectively), which signified a steady change in the distribution of the expression with a declining differentiation status (Tab. 2).

**Table 2.**

MIF Expression across Histological Grades

| Histological Grade | Mean±SD | Median | Min | Max |
|---|---|---|---|---|
| Well Differentiated | 10.58±0.60 | 10.62 | 8.41 | 11.61 |
| Moderate Differentiation | 10.78±0.71 | 10.83 | 8.04 | 12.72 |
| Poorly Differentiated | 11.05±0.68 | 11.09 | 8.43 | 12.46 |

In order to analyse further the fluctuation of MIF expression level in the diverse levels of tumour differentiation, the average expression levels were plotting in the histological grades (Fig. 2).

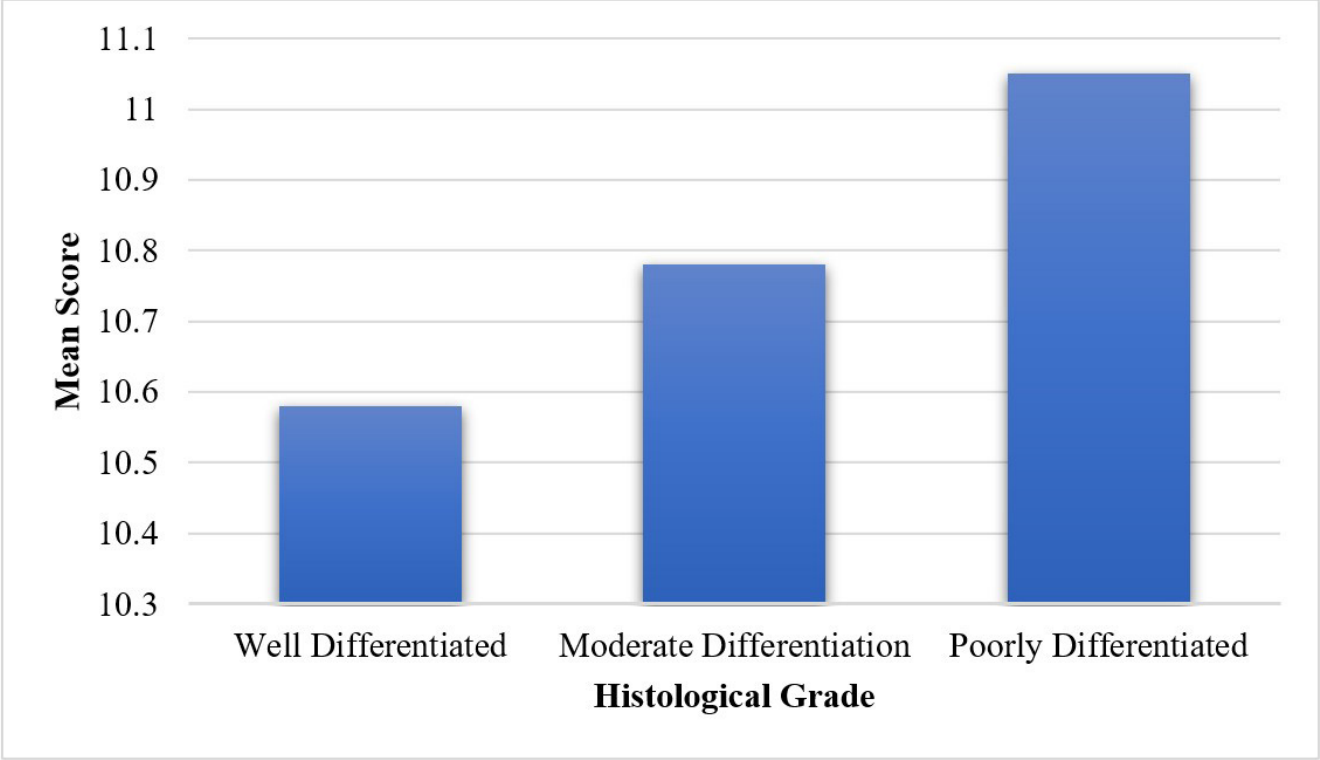


**Fig. 2. Mean MIF Expression across Histological Grades**

Fig.2 shows that MIF expression gradually rises as the differentiation is lower, showing that there is a positive correlation between MIF levels and tumour aggressiveness. The gradual progression of well differentiated to poorly differentiated tumours is an indication that MIF expression correlated to some biological alterations that accompany tumour progression. The trend supports the statistically observed disparities and indicates the possibility of MIF during advanced disease conditions.

*Pairwise Comparison of MIF Expression Using Independent t-tests.* The t-tests by Independent Welch indicated statistically significant differences in the MIF expression between all the histological groups. There was a very significant difference between the poorly and well-differentiated tumours and the poorly and moderately differentiated tumours. As well, there was a statistically significant difference in moderately and well-differentiated tumours (t=2.10, p=0.04) (Tab. 3).

**Table 3.**

Independent t-test Results

| Comparison | t-value | p-value | Significance |
|---|---|---|---|
| Poor vs Well Differentiated | 5.08 | $1.696\times10^{-6}$ | Highly significant |
| Poor vs Moderate | 3.92 | $1.063\times10^{-4}$ | Highly significant |
| Moderate vs Well | 2.10 | 0.04 | Significant |

*Correlation Analysis of MIF Expression with Clinical Risk.* The Pearson correlation analysis found out that MIF expression and clinical risk status had weak positive association (r=0.06); although not statistically significant (p=0.20) (Tab. 4).

**Table 4.**

Correlation Analysis

| Variable Pair | Correlation Coefficient (r) | p-value | Interpretation |
|---|---|---|---|
| MIF vs High Risk | 0.06 | 0.20 | Weak, non-significant |

*Regression Analysis of MIF Expression as a Predictor of Clinical Risk.* However, it was revealed by linear regression analysis that MIF expression did not have statistically significant predictive value in clinical risk (β=0.04, p=0.20). This model demonstrated a very low explanatory power ($R^2$=0.003), which means that MIF expression has a little contribution to clinical risks prediction. The intercept value was also not significant (β=–0.08, p=0.84) (Table 5).

**Table 5.**

Linear Regression Results

| Parameter | Coefficient (β) | Standard Error | t-value | p-value |
|---|---|---|---|---|
| Intercept | –0.08 | 0.36 | –0.21 | 0.84 |
| MIF Expression | 0.04 | 0.03 | 1.29 | 0.20 |
| **$R^2$** | **0.003** | | | |
| **Adjusted $R^2$** | **0.001** | | | |

**Discussion.** The study is an exploratory study of MIF in lung disease through gene expression profiling based on the microarray. The results showed a steady rise in MIF expression as histological differentiation diminished suggesting that there may be some correlation between high levels of MIF and tumour aggressiveness. This tendency indicates that MIF can be involved in the pathophysiology of tumour processes in general and poor differentiation in particular tumours that commonly linked to later and more aggressive forms of the disease. The observed statistically significant differences between the histological groups are another factor supporting the applicability of the MIF as a tumour differentiation marker.

Notwithstanding this connection, the research study has shown that the expression of MIF is not significantly related to clinical risk as reflected by

the null and weak association and the small amount of explanatory information of the regression analysis ($R^2$=0.003). This shows that expression of MIF varies amongst different levels of tumour differentiation, but it has no significant value in forecasting clinical risks outcomes. Thus, it concluded that MIF is a biological indicator of tumour behaviour, but not a prognostic indicator because the interactions between molecules complicate the situation of lung cancer and require multi-marker solutions in the risk prediction.

The current finding of the enhanced expression of MIF in the more aggressive tumour phenotypes compared to the previous research, which has also demonstrated the importance of MIF and the associated immune pathways in the progression of the disease. The study by Saul et al. [19] showed that cellular senescence gene sets are connected to inflammatory- and stress-response mechanisms across all tissues, which can be interpreted as suggesting that high levels of MIF can be indicative of a wider range of biological reaction in disease. Spiller et al. [20] also demonstrated that MIF is an antagonist of CXCR2 and CXCR4 receptors and that MIF interacts with receptor-mediated cytokine signaling and immune cell communication, which could be a possible factor in its up regulation in aggressive tumours. Likewise, Sweatt et al. [21] have determined that pulmonary disease has unique immune phenotypes, and the role of immune mediators in the heterogeneity of the disease is significant. According to Swoboda et al. [22] changes in the MIF levels were observed in systemic conditions, which means that it is not involved in the inflammatory regulation in one specific disease situation. Furthermore, Tamò et al. [23] emphasized the interplay between the cellular secretes and the macrophage activity, which implies that MIF might be a component of a complex network that affects immune response. Wang et al. [24] and Xie et al. [25] further reinforced the latter in recent works, which suggested the idea that MIF was not a single predictor but rather a part of an extended immunological mechanism of relationships between the tumour microenvironment and its own response to therapy. In general, these works substantiate the results of the current analysis, according to which, MIF expression linked to tumour differentiation, but does not have good predictive capability of clinical risk.

These implications are important as far as cancer biology and biomarker studies are concerned. The correlation of MIF with tumour differentiation indicates that it can be an effective predictor of tumour aggressiveness and inflammatory activity, which used in the biological characterization of lung cancer. Nonetheless, its poor predictability of clinical risk highlights the drawback of using single-gene markers to predict clinical risk. Moreover, the knowledge of MIF involvement in tumour-associated inflammation used to inform about potential therapeutic modulators, especially those that focus on tumour microenvironment modulation.

There are some limitations of the study that should be admitted. To begin with, the study reviewed one secondary data, which might reduce the ability to generalize the results to various groups of people and clinical environments. Second, microarray data (though a universally accepted method) have an intrinsic sensitivity and dynamic range disadvantage over next-generation sequencing methods. Third, the paper was devoted to one gene (MIF) without the consideration of the whole range of interacting genes and pathways, which can affect the obtained results. In addition, cross-sectional characteristics of the data cannot be used to conclude on the causation between MIF expression and the development of the disease.

Further studies are necessary in an attempt to corroborate these results with independent datasets and cohorts of larger sizes, with RNA sequencing results possibly being included in the future where more accuracy achieved. Comprehensive analyses of the role of MIF in lung disease could be achieved by integrative analyses of numerous genes and studies at the pathway level. Additionally, longitudinal research studies regarding the variation in MIF expression with time and on different treatments may also provide useful information on its usefulness as a dynamic biomarker. The study of the interplay of MIF and immune signalling pathways and the tumour microenvironment could also be beneficial in identifying new therapeutic targets and enhancing individualized treatment plans.

In summary, the current research paper shows that, MIF expression is largely linked to tumour differentiation in lung disease, which indicates its role in tumour biology/inflammatory. The weaknesses of BATF, however, in its inability to predict clinical risk are an important aspect, which requires multi-dimensional development of biomarkers. These results promote the ever-growing knowledge of the multifaceted role of MIF in cancer

and the significance of the combined molecular and clinical data in the context of translational research.

**Conclusion.** The present study gives an exploratory assessment of the expression of Macrophage Migration Inhibitory Factor in lung disease through gene expression profiling. The results also establish that MIF persistently expressed in the lung tissue samples, and it significantly increased in samples with reduced histological differentiation, which reveals that MIF closely tied to aggregate tumour aggressiveness. The continuous increase in the expression of MIF with well-differentiated and poorly differentiated tumours makes MIF a possible participant in the biological processes of tumour progression and inflammatory response. Statistical analysis also proved the differences in the MIF expression in the histological grades are significant, proving its applicability as a tumour differentiation marker. Nonetheless, in spite of this correlation, the analysis did not show any significant relationship between MIF expression and clinical risk and the regression analysis showed that predictive ability was low with insignificant explanatory ability. These findings indicate that although MIF is a part of the tumour biology, it is not a prognostic independent variable that can be used to predict clinical risks. In general, the main results suggest that MIF regarded as a biological marker of the severity of tumour but not a clinical outcome predictor biomarker. This implies that lung cancer is a complicated condition and that multi-marker methods should be used in prognostic evaluation. The combination of MIF with other molecular and clinical parameters in the future could be more useful in relation to disease progression, as well as the development of individual therapeutic options.

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## XÜLASƏ

## AĞCİYƏR XƏSTƏLİKLƏRİNDƏ MAKROFAQLARIN MİQRASİYASINI İNHİBƏ EDƏN FAKTORUN EKSPRESSİYASI: GEN EKSPRESSİYASI PROFİLLƏŞDİRİLMƏSİNDƏN İSTİFADƏ ETMƏKLƏ EKSPLORATİV TƏDQİQAT

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Makrofaq miqrasiyası İnhibitoru Faktoru (MIF) immun tənzimlənmə və şiş biologiyasında iştirak edən əsas iltihab sitokinidir. Ağciyər xəstəliyində, xüsusən də şiş diferensiasiyası və klinik risklə əlaqəli rolu hələ də tam aydınlaşdırılmamışdır. Bu tədqiqatın məqsədi gen ekspressiyası profilindən istifadə edərək ağciyər xəstəliyiklərində MIF-in ekspressiyasını, histoloji dərəcələr

üzrə dəyişkənliyini qiymətləndirmək və klinik risklə əlaqəsini müəyyən etməkdir. İctimaiyyətə açıq məlumat mənbəyindən əldə edilən 442 ağciyər toxuması nümunəsindən mikroarray gen ekspressiyası məlumatları istifadə edilərək ikinci dərəcəli məlumatlara əsaslanan analitik təhlili aparılmışdır. MIF ekspressiyası Affymetrix İnsan Genomu U133A platformasından zond ID 200799_at istifadə edilərək çıxarılmışdır. Nümunələr histoloji diferensiasiyasına əsasən yaxşı, orta və zəif diferensiasiya olunmuş qruplara bölünmüşdür. Statistik təhlillərə təsviri statistika, Welch t-testi, Pearson korrelyasiyası və xətti reqressiya daxil edilmişdir. MIF ekspressiyası şiş diferensiasiyasının azalması ilə əhəmiyyətli dərəcədə artım nümayiş etdirərək, ən yüksək səviyyələr zəif diferensiasiya olunmuş şişlərdə müşahidə edilmişdir (11,05±0,68). Müstəqil t-testlər bütün histoloji qruplar arasında əhəmiyyətli fərqləri təsdiqlədi ($p<0,05$). Lakin korrelyasiya təhlili klinik risklə zəif və əhəmiyyətsiz bir əlaqəni ortaya qoydu ($r=0,06$, $p=0,20$) və reqressiya təhlili minimal proqnozlaşdırma gücünü göstərdi ($R^2=0,003$). MIF ekspressiyası ağciyər xəstəliyində şiş diferensiasiyası ilə əhəmiyyətli dərəcədə əlaqələndirilir, lakin klinik risk üçün proqnozlaşdırma dəyəri yoxdur. Bu məlumatlar MIF-in müstəqil proqnostik biomarker deyil, şiş biologiyasının markeri kimi xidmət etdiyini göstərir.

**Açar sözlər:** makrofaq miqrasiyası inhibitoru faktoru, ağciyər xərçəngi, gen ekspressiyası, şiş diferensiasiyası

## РЕЗЮМЕ

# ЭКСПРЕССИЯ ФАКТОРА ИНГИБИРОВАНИЯ МИГРАЦИИ МАКРОФАГОВ ПРИ ЗАБОЛЕВАНИЯХ ЛЁГКИХ: ЭКСПЛОРАТОРНОЕ ИССЛЕДОВАНИЕ С ИСПОЛЬЗОВАНИЕМ ПРОФИЛИРОВАНИЯ ЭКСПРЕССИИ ГЕНОВ

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Фактор ингибирования миграции макрофагов (MIF) – ключевой воспалительный цитокин, участвующий в регуляции иммунитета и биологии опухолей. Его роль в заболеваниях легких, особенно в отношении дифференцировки опухолей и клинического риска, остается недостаточно изученной. Целью данного исследования было оценить характер экспрессии MIF при заболеваниях легких с использованием профилирования экспрессии генов, оценить его вариабельность в зависимости от гистологической степени и определить его связь с клиническим риском. Был проведен вторичный исследовательский анализ на основе данных микроматричного анализа экспрессии генов из 442 образцов легочной ткани, полученных из общедоступного набора данных. Экспрессия MIF была выделена с использованием зонда ID 200799_at с платформы Affymetrix Human Genome U133A. Образцы были стратифицированы на основе гистологической дифференцировки на группы с хорошей, умеренной и плохой дифференцировкой. Статистический анализ включал описательную статистику, t-критерий Уэлча, корреляцию Пирсона и линейную регрессию. Экспрессия MIF продемонстрировала значительное увеличение с уменьшением степени дифференцировки опухоли, при этом самые высокие уровни наблюдались в низкодифференцированных опухолях (11,05±0,68). Независимые t-тесты подтвердили значительные различия между всеми гистологическими группами ($p<0,05$). Однако корреляционный анализ выявил слабую и незначимую связь с клиническим риском ($r=0,06$, $p=0,20$), а регрессионный анализ показал минимальную прогностическую силу ($R^2=0,003$). Экспрессия MIF значительно связана с дифференцировкой опухоли при заболеваниях легких, но не обладает прогностической ценностью для клинического риска. Эти результаты позволяют предположить, что MIF служит маркером биологии опухоли, а не самостоятельным прогностическим биомаркером.

**Ключевые слова:** фактор ингибирования миграции макрофагов, рак легких, экспрессия генов, дифференцировка опухоли

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