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EXPRESSION PROFILES OF CYP1A1 AND CYP1B1 ENZYMES IN NON-SMALL CELL LUNG CANCER OF TURKISH PATIENTS

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Abstract

Background. The cytochrome P450 enzymes CYP1A1 and CYP1B1 are involved in the metabolism of carcinogens and have been linked to various cancers, including lung cancer, primarily through their overexpression in tumor tissues. **Aim of study.** This study describes the CYP1A1 and CYP1B1 expression profiles in lung adenocarcinoma (AC) and lung squamous cell carcinoma (SCC), and explores the possible associations with demographic and clinical features among Turkish patients. **Material and Methods.** This retrospective study analyzed clinical data from 40 patients with lung adenocarcinoma and lung squamous cell carcinoma. Tumor and adjacent healthy tissue samples were immunohistochemically stained to profile CYP1A1 and CYP1B1 expression. Associations between protein expression levels and patient characteristics were examined. **Results.** Significant immunohistochemical differences were found between tumorous and healthy tissues for CYP1A1 and CYP1B1. **Conclusion.** The study suggests that the CYP1A1 and CYP1B1 expression profiles in lung adenocarcinoma and lung squamous cell carcinoma among Turkish patients may have biomarker value for risk stratification and early detection.

Key words: Cytochrome P450 enzymes, CYP1A1, CYP1B1, Non-small Cell Lung Cancer.

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ПРОФИЛИ ЭКСПРЕССИИ ФЕРМЕНТОВ CYP1A1 И CYP1B1 ПРИ НЕМЕЛКОКЛЕТОЧНОМ РАКЕ ЛЕГКОГО У ТУРЕЦКИХ ПАЦИЕНТОВ

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Аннотация

Актуальность. Ферменты цитохрома P450 CYP1A1 и CYP1B1 участвуют в метаболизме канцерогенов и связаны с различными видами рака, включая рак легкого, в основном за счет повышенной экспрессии в опухолевых тканях. **Цель исследования –** оценка уровней экспрессии CYP1A1 и CYP1B1 при аденокарциноме и плоскоклеточном раке легкого, а также их связи с демографическими и клиническими показателями у турецких пациентов. **Материал и методы.** В ретроспективном исследовании проведен сравнительный анализ клинических данных 40 пациентов с аденокарциномой и плоскоклеточным раком легкого. Уровни экспрессии CYP1A1 и CYP1B1 оценивались при иммуногистохимическом исследовании образцов опухоли и прилегающих здоровых тканей. Изучены ассоциации между уровнями экспрессии белка и клинико-морфологическими характеристиками пациентов. **Результаты.** Обнаружены значительные иммуногистохимические различия в уровнях экспрессии генов CYP1A1 и CYP1B1 между опухолевыми и здоровыми тканями. **Заключение.** Профили экспрессии CYP1A1 и CYP1B1 в образцах аденокарциномы и плоскоклеточной карциномы легкого могут быть потенциальными биомаркерами для стратификации риска и раннего выявления рака.

Ключевые слова: ферменты цитохрома P450, CYP1A1, CYP1B1, немелкоклеточный рак легкого.

Introduction

Tumors originating in the lung parenchyma or bronchi are termed lung cancer or bronchogenic carcinoma [1]. Lung neoplasms are the foremost contributors to both cancer incidence and mortality worldwide. In 2022, lung cancer emerged as the predominant malignancy globally, with approximately 2.5 million new cases, accounting for 12.4 % of the total cancer incidence. Furthermore, it exhibited the highest fatality rate among cancer types, causing about 1.8 million deaths, representing 18.7 % of all cancer-related mortalities [2].

Advancements in diagnostic techniques have significantly enhanced the precision of pathological and genetic classifications of lung tumors, facilitating the development of more effective therapeutic interventions. This progress is largely attributable to the integration of immunohistochemistry and molecular testing into classification protocols. The 2021 WHO Classification of Thoracic Tumors encompasses a comprehensive range of categories, including papillomas, adenomas, precursor glandular lesions, lung adenocarcinoma in situ, lung adenocarcinomas (AC), invasive nonmucinous lung adenocarcinoma, squamous precursor lesions, lung squamous cell carcinomas (SCC), large cell carcinomas (LCC), adenosquamous carcinomas, sarcomatoid carcinomas, neuroendocrine tumors, salivary gland-type tumors, neuroendocrine carcinomas (including small cell carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNEC)), tumors of ectopic tissues (melanoma and meningioma), mesenchymal tumors specific to the lung, and PEComatous tumors [3]. AC, SCC, and LCC are subtypes of non-small-cell lung carcinoma (NSCLC), which represents 85 % of all lung cancer cases [4].

Lung adenocarcinomas are pathologically distinguished by the formation of neoplastic glands, the presence of pneumocyte markers such as thyroid transcription factor 1 (TTF-1) with or without napsin expression, and intracytoplasmic mucin. Squamous cell pathology is identified by the presence of keratin and/or intercellular desmosomes [5].

CYP1A1 and CYP1B1 are enzymes belonging to the cytochrome P450 superfamily, playing significant roles in the metabolism of various carcinogens. CYP1A1 is primarily involved in the biotransformation of polycyclic aromatic hydrocarbons (PAHs) and other carcinogens. Its expression is notably higher in lung tissues exposed to environmental carcinogens and has been identified as a key player in lung carcinogenesis. CYP1A1 is markedly induced by PAHs, leading to increased DNA adduct formation, which is a critical step in the initiation of cancer. Elevated levels of CYP1A1 expression have been associated with a higher risk of lung cancer. In lung cancer tissues, CYP1A1 has been detected in a substantial proportion of lung adenocarcinomas, suggesting its potential role as a biomarker for lung cancer [6, 7]. CYP1B1 has been identified as a potential tumor marker, often overexpressed in various tumor tissues, including lung cancers, while being absent in normal tissues. This differential expression underscores its potential utility in cancer diagnostics and as a therapeutic target [6, 8].

Although CYP1A1 and CYP1B1 are known to be involved in the metabolism of carcinogens, their exact roles in lung cancer warrant further investigation. Particularly, studying the variability of CYP1A1 and CYP1B1 expression in lung tissues from different individuals and correlating this with clinical outcomes could help identify potential biomarkers for lung cancer prognosis. Hence, this study addresses the CYP1A1 and CYP1B1 expression profiles in two distinct types of NSCLC tumor samples: lung adenocarcinoma (AC) and lung squamous cell carcinoma (SCC), and explores the possible association with demographic and clinical features among Turkish patients.

Material and Methods

This study performed a retrospective analysis of clinical data from patients with lung adenocarcinomas and lung squamous cell carcinomas treated at the Dr. Lütfi Kırdar Education and Research Hospital's Pathology Clinic between 2017 and 2019. Archival sampling was carried out among patients who met the study's inclusion and exclusion criteria, resulting in the recruitment of 40 subjects (20 lung AC and 20 lung SCC) aged 46 to 83 years (mean 67.20 ± 8.5 years), with a gender distribution of 11 females and 29 males, representing the broader population. Each patient's cancer stage was determined at the time of surgery using the TNM staging method by the American Joint Committee on Cancer. Of the 40 surgically removed lung tumors, 13 were stage 1A, 7 were stage 1B, 8 were stage 2A, 9 were stage 2B, and 3 were stage 3A, with an average tumor diameter of 3.67 ± 0.38 cm. Histopathological analysis of the tumors and adjacent healthy tissues was conducted using immunohistochemical (IHC) staining to profile CYP1A1 and CYP1B1 enzymes.

Inclusion and exclusion criteria

Patients with NSCLC tumor samples, including lung adenocarcinomas and lung squamous cell carcinomas, were considered for the investigation if both tumor and adjacent healthy tissue samples were available. Additionally, patients should not have received any prior treatment for NSCLC, such as chemotherapy, radiation therapy, or surgery. Therefore, patients meeting these criteria, with sufficient clinical and pathological data listed in Table 1, were included in the study.

To ensure validity, exclusion criteria were applied to exclude patients with small cell lung cancer (SCLC), other histological types of lung cancer, or a history of other malignancies. Moreover, patients with severe comorbidities that might affect the interpretation of the study results, such as severe cardiovascular disease, liver or kidney failure, or autoimmune disorders, were excluded from the sample group.

Data collection

Demographic and clinical information was meticulously collected using a detailed checklist that included parameters such as age, gender, diagnosis, tumor grade, localization, presence of vascular and neural invasion, bronchial and pleural involvement, in situ status, metastasis, tumor size, lymph node involvement, stage, neoadjuvant therapy, and survival status. This comprehensive data collection enabled a thorough retrospective analysis of each subject's background. Tumor and adjacent healthy tissue samples were obtained from surgical sites following standardized protocols by skilled surgeons and preserved in paraffin for subsequent analysis. Immunohistochemical (IHC) methods were employed to evaluate the expression levels of CYP1A1 and CYP1B1 proteins.

Histopathological analysis of tissue is crucial for providing detailed insights into tumor characteristics, essential for accurate diagnosis, classification, and prognosis. This process begins with the procurement of tissue during surgical resection, followed by immersion in 10 % buffered formalin for preservation. Thin sections, 4 μm thick, are prepared by embedding the tissue in paraffin wax using a microtome. These sections are then mounted on glass slides and stained with hematoxylin and eosin to analyze tissue morphology. Additionally, immunohistochemical (IHC) staining is performed to detect the expression of CYP1A1 and CYP1B1 proteins. This comprehensive analysis aids in making informed therapeutic decisions and predicting prognosis based on the tumor's molecular profile.

For immunohistochemical staining, the formalin-fixed, paraffin-embedded tissues sections, after deparaffinization, were incubated for 10 minutes at room temperature in a 3 % hydrogen peroxide (v/v) in methanol solution to neutralize the natural peroxidase activity. After that, the parts were given a five-minute rinse with distilled water. Using 0.01 M citrate buffer (pH 6.0), antigen retrieval was carried out for three minutes using a home pressure cooker. To avoid non-specific background staining, the sections were treated for 10 minutes at room temperature with super block (SHP125) from ScyTek Laboratories, USA. The sec-

Table 1/Таблица 1

Demographic and clinical data of patients

Демографические и клинические данные пациентов

Parameteres/Показатели	Number of patients/Число больных
Demographic data/Демографические данные	
Gender/Пол	
Female/Жен	11 (27.5 %)
Male/Муж	29 (72.5 %)
Age/Возраст	
≤65 years/лет	15 (37.5 %)
>65 years/лет	25 (62.5 %)
Clinical data/Клинические данные	
Diagnosis/Диагноз	
Lung adenocarcinoma/Аденокарцинома легкого	20 (50 %)
Squamous cell carcinoma/Плоскоклеточный рак	20 (50 %)
Grade/Гистологический тип	
Acinar/Ацинарный	5 (12.5 %)
Keratinized/Ороговевший	10 (25.0 %)
Lepidic/Лепидический	5 (12.5 %)
Non-keratinized/Неороговевший	10 (25.0 %)
Papiller/Папиллярный	5 (12.5 %)
Solid/Солидный	5 (12.5 %)
Localization/Локализация	
Right adenocarcinoma/Аденокарцинома правого легкого	1 (2.5 %)
Right lower lobe/Правая нижняя доля легкого	11 (27.5 %)
Right upper lobe/Правая верхняя доля	12 (30.0 %)
Left adenocarcinoma/Аденокарцинома левого легкого	2 (5.0 %)
Left lower lob/Левая нижняя доля	2 (5.0 %)
Left upper lob/Левая верхняя доля	11 (27.5 %)
Upper lobe/Верхняя доля	1 (2.5 %)
Vascular invasion/Васкулярная инвазия	
Yes/Да	13 (32.5 %)
No/Нет	27 (67.5 %)
Neural invasion/Периневральная инвазия	
Yes/Да	9 (22.5 %)
No/Нет	31 (77.5 %)
Bronchial involvement/Поражение бронхов	
Yes/Да	11 (27.5 %)
No/Нет	29 (72.5 %)
Pleural involvement/Поражение плевры	
Yes/Да	12 (30.0 %)
No/Нет	28 (70.0 %)
Cancer in situ	
Yes/Да	4 (10.0 %)
No/Нет	36 (90.0 %)
Metastasis/Метастаз	
Yes/Да	13 (32.5 %)
No/Нет	27 (67.5 %)
Tumor size/Размер опухоли	
T1A	11 (27.5 %)
T1B	5 (12.5 %)
T2A	12 (30.0 %)
T2B	4 (10.0 %)
T3	8 (20.0 %)
Lymph Node metastasis/Метастазы в лимфоузлы	
N0	29 (72.5 %)
N1	7 (17.5 %)
N2	3 (7.5 %)
No data/Нет данных	1 (2.5 %)
Stage/Стадия	
1A	13 (32.5 %)
1B	7 (17.5 %)
2A	8 (20.0 %)
2B	9 (22.5 %)
3A	3 (7.5 %)
Survival status/Статус выживаемости	
Dead/Умерли	9 (22.5 %)
Alive/Живы	31 (77.5 %)

Notes: created by the authors.

Примечания: таблица составлена авторами.

tions were then covered with the primary antibodies diluted (1:100 for CYP1A1; 1:100 for CYP1B1) in TBS at 4 °C. Anti CYP1A1 (sc-20,772) and Anti-CYP1B1 (sc-32,882) were obtained from Santa Cruz Biotechnology Inc., Dallas, TX.

The sections were washed in TBS before being incubated for 10 minutes at room temperature for the biotinylated link antibody (SHP125) (ScyTek Laboratories, USA). Next, the sections were washed in TBS before they were incubated for 10 minutes at room temperature with streptavidin/HRP complex (SHP125) (ScyTek Laboratories, USA). Diaminobenzidine (DAB) was used to monitor the peroxidase activity. After a brief counterstain with hematoxylin, the sections were dried and mounted.

The following scale was used to measure to evaluate the immunoreactivity for cancer cells for CYP1A1, and CYP1B1 enzymes: (0) for negative staining (no protein expression), (+1) for weak staining, (+2) for moderate staining (moderate level of protein expression), and (+3) for strong staining (strong level of protein expression) (Fig. 1).

All statistical analyses were conducted using the R project for statistical computing version 4.3.2

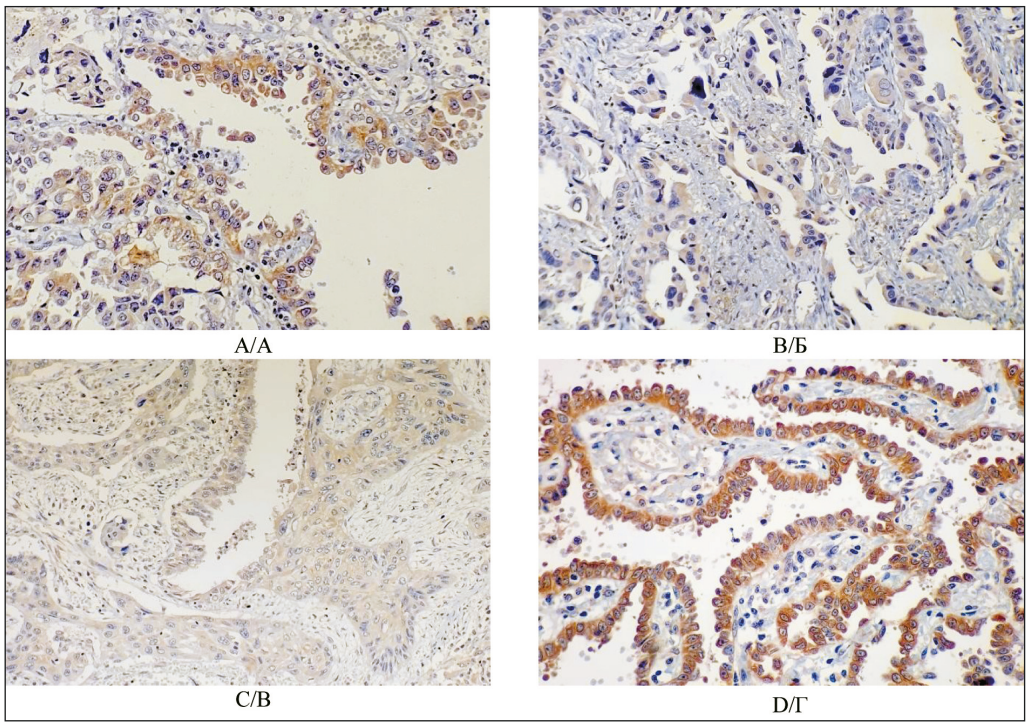

Fig. 1. Microphoto. Immunohistochemical staining of non-small cell lung cancer tissue. Notes: A – CYB1A1, Shows expression score +1, ×400; B: CYB1A1, Shows expression score +2, ×400; C: CYB1B1, Shows expression score +1, ×400; D: CYB1B1,Shows expression score +3, ×400. Note: created by the authors

Рис. 1. Микрофото. Иммуногистохимическое исследование. Немелкоклеточный рак легкого. Примечания: А – CYB1A1, уровень экспрессии +1, ×400; Б – CYB1A1, уровень экспрессии +2, ×400; В – CYB1B1, уровень экспрессии +1, ×400; D – CYB1B1, уровень экспрессии +3, ×400. Примечание: рисунок выполнен авторами

(R Foundation, Vienna, Austria). Our investigation included normal tissues and SCC and AC tumours from 40 patients. Continuous data were summarized as the mean ± standard deviation, while categorical data were presented as frequencies (n) accompanied by relative frequencies (%). The Shapiro–Wilk test assessed the distribution patterns of the data, while the Levene test examined homogeneity of variances. The Mann–Whitney U test compared pairs when parametric test assumptions were not met. The Chi-square test investigated associations between categorical variables. Spearman's rank correlation test was used for correlation analyses. Additionally, the relationship between the protein expression and survival rates of the studied patients was exacuted using the Kaplan-Meier method while categorize expression into high and low using median as the cutoff. All statistical analyses were performed at a 95 % confidence level.

Results

CYP1A1 and CYP1B1 expressions were examined immunohistochemically, with their expression levels summarized in Table 2. While CYP1A1 expression was undetected in the vast majority of healthy tissues (97.5 %), significant expression was observed in 47.5 % of tumorous tissues (35.0 % weak; 12.5 % moderate) (p=0.0005). Similarly, CYP1B1 expression was detected in 80.0 % of tumorous tissues, at low (47.5 %), moderate (25.5 %), or high (5 %) levels. In contrast, only 2.5 % of healthy tissues showed low-level expression, indicating a significant increase in CYP1B1 expression in tumorous tissues (p<0.00001). Furthermore, a significant positive correlation was observed between CYP1A1 and CYP1B1 expressions (r_s=0.35, p=0.02).

The Kaplan–Meier Survival Estimates table presents the survival probabilities for different expression groups of CYP1A1 and CYP1B1 over time, measured in months (Table 3). The analysis includes time intervals ranging from 1 to 43 months. Patients with high levels of CYP1A1 protein expression demonstrate a survival probability that decreases over time, with a survival probability of 94.7 % at 1 month, decreasing to 58.6 % at 36 months. In contrast, individuals with low CYP1A1 expression start with a survival probability of 96.3 % at 1 month, showing a gradual decline to 67.4 % by 43 months. Overall, the low CYP1A1 expression profile exhibits higher survival probabilities compared to the high expression across all time points.

The survival probability among patients with higher CYP1B1 expression begins at 92.3 % at 19 months and falls to 70.5 % at 36 months, indicating a declining trend over time. In the low expression group, a survival probability of 96.3 % is observed at 1 month, which decreases more gradually over time, reaching a survival probability of 67.4 % at 43 months. This again shows a trend toward higher survival compared to the high expression group.

Table 2/Таблица 2

Immunohistochemically detected CYP1A1, and CYP1B1 expression levels of tumor and normal tissues

Уровни экспрессии CYP1A1 и CYP1B1 в опухоли и нормальной ткани по данным иммуногистохимического исследования

IHC Score/ Уровень экспрессии	CYP1A1		CYP1B1	
	Tumor/ Опухолевая ткань	Normal/ Нормальная ткань	Tumor/ Опухолевая ткань	Normal/ Нормальная ткань
0	21/40 (52.5 %)[a]	39/40 (97.5 %)[a]	8/40 (20 %)[a]	39/40 (97.5 %)[a]
1	14/40 (35.0 %)[a]	1/40 (2.5 %)[a]	19/40 (47.5 %)[a]	1/40 (2.5 %)[a]
2	5/40 (12.5 %)[a]	–	11/40 (27.5 %)[a]	–
3	–	–	2/40 (5%)[a]	–
Mean/ Среднее значение	0.6 ± 0.1 (0–2)[c]	0.02 ± 0.02 (0–1)[c]	1.17 ± 0.12* (0–3)[c]	0.02 ± 0.02 (0–1)[c]
p–value	0.0005		<0.00001	

Notes: total n=40; scoring was made according to the staining intensity of the tissues: 0 – no staining, 1 – weak positive, 2 – moderate positive, 3 – strong positive; * – statistically significant according to the Mann–Whitney U test ($p<0.05$); [a] – number of samples stained at the specified score/ total number of samples; [b] – Mean ± SE; [c] – min – max; created by the authors.

Примечания: n=40; интенсивность окрашивания тканей: 0 – отсутствие, 1 – слабоположительная, 2 – умеренно положительная, 3 – высоко положительная; * – различия статистически значимые согласно U–критерию Манна–Уитни ($p<0,05$); [a] – количество образцов, окрашенных по указанной шкале/общее количество образцов; [b] – Среднее ± SE; [c] – мин–макс; таблица составлена авторами.

Table 3/Таблица 3

Kaplan–Meier Survival Estimates

Оценки выживаемости по методу Каплана–Майера

Time (Months)/ Сроки наблюдения (мес)	CYP1A1 Expression Group/ Экспрессия CYP1A1		CYP1B1 Expression Group/ Экспрессия CYP1B1	
	Survival/ Выживаемость	95 % CI	Survival/ Выживаемость	95 % CI
1	94.7 %	85.2–100 %	96.3 %	89.4–100 %
19	89.5 %	76.7–100 %	92.3 %	78.9–100 %
22	84.2 %	69.3–100 %	84.6 %	67.1–100 %
29	78.2 %	61.3–99.7 %	84.7 %	71.8–99.8 %
36	58.6 %	36.7–93.7 %	70.5 %	46.0–100 %
43	72.4 %	45.7–100 %	67.4 %	46.4–97.9 %

Note: created by the authors.

Примечание: таблица составлена авторами.

In general, the high expression groups for both CYP1A1 and CYP1B1 exhibit lower survival probabilities over time compared to the low expression groups (Fig. 2, 3). The log-rank test results for CYP1A1 ($p=0.2$) and CYP1B1 ($p=0.8$) suggest that the observed differences in survival between high and low protein expression groups are not strong enough to conclude a significant difference in survival rates (Fig. 2, 3).

The study also investigated the association between demographic and clinical data and the expression levels of CYP1A1 and CYP1B1. No significant association, and correlation was found between demographic or clinical variables and the expression levels of CYP1A1 and CYP1B1 ($p>0.05$).

Discussion

The cytochrome P450 enzymes CYP1A1 and CYP1B1 are involved in the metabolism of carcinogens and have been linked to various cancers, including lung cancer, primarily through their overexpression in tumor tissues [8]. The results of the current study enhance our understanding of the roles of CYP1A1 and CYP1B1 in carcinogenesis within NSCLC tumor tissues. Specifically, for the first time, the expression profiles of CYP1A1 and CYP1B1 in lung AC and lung SCC tissues from Turkish patients have been revealed.

The study findings indicate that CYP1A1 expression is significantly elevated in a substantial proportion of lung AC and lung SCC tissues. The notable expression of CYP1A1 in nearly half of the NSCLC tumor tissues highlights its crucial role in NSCLC. Previous research has shown that high levels of CYP1A1 are observed in lung AC and lung SCC tissues, particularly in smokers, compared to normal lung tissues [9, 10]. This suggests that CYP1A1 could serve as a potential biomarker for the presence of lung AC and lung SCC.

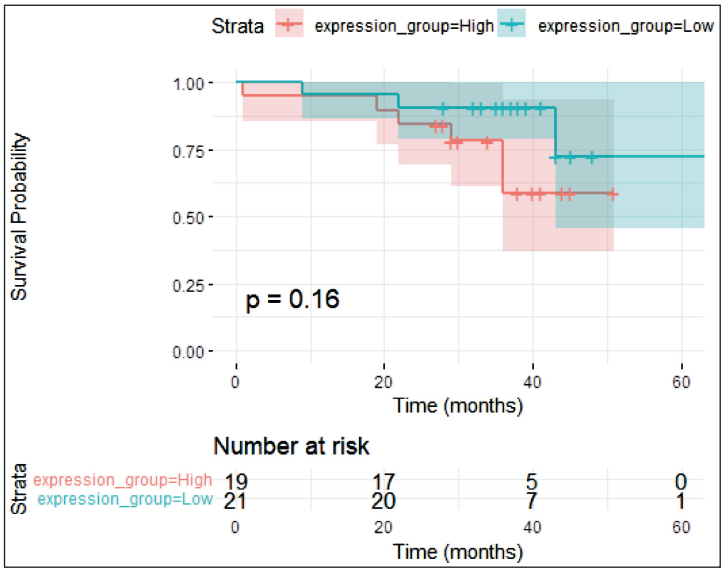

Fig. 2. Kaplan–Meier survival curve comparing high *vs* low CYP1A1 expression in patients.
Note: created by the authors
Рис. 2. Показатели выживаемости по Каплану–Майеру в зависимости от уровня экспрессии CYP1A1. Примечание: рисунок выполнен авторами

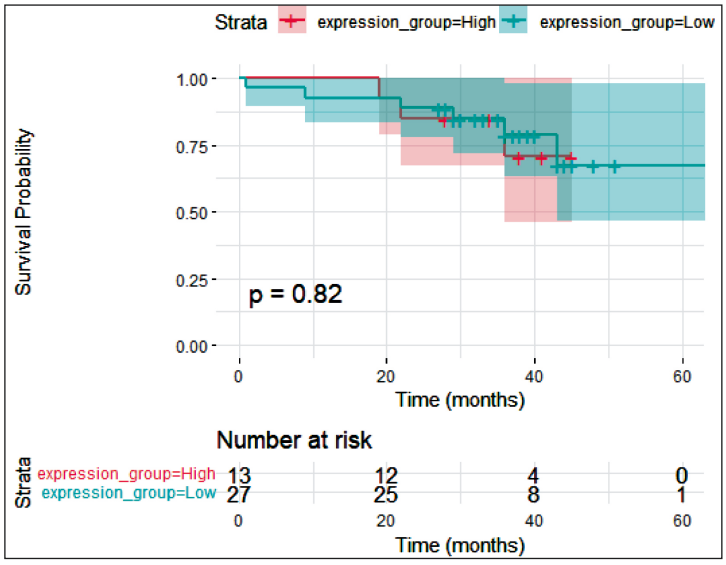

Fig. 3. Kaplan–Meier survival curve comparing high *vs* low CYP1B1 expression in patients.
Note: created by the authors
Рис. 3. Показатели выживаемости по Каплану–Майеру в зависимости от уровня экспрессии CYP1B1. Примечание: рисунок выполнен авторами

Moreover, CYP1B1 expression is significantly elevated in a large proportion of lung tumor tissues. Specifically, CYP1B1 was expressed at varying levels (low, moderate, or high) in 80.0 % of the tumorous tissues examined. Studies have demonstrated CYP1B1 overexpression in various malignancies, including NSCLC [11–13]. The high prevalence of CYP1B1 expression suggests that this enzyme plays a widespread role in lung cancer biology. In lung adenocarcinoma tissues, CYP1B1 expression has been associated with increased tumor aggressiveness. Research indicates that high levels of CYP1B1 correlate with poor prognosis and may contribute to the bioactivation of carcinogens, leading to DNA damage and tumor development. Similarly, in lung SCC, CYP1B1 has been found to be upregulated, with its expression linked to mechanisms of drug resistance [11, 12]. Given its significant expression in the majority of tumorous tissues, CYP1B1 could serve as a valuable biomarker for detecting lung AC and lung SCC, aiding in diagnosis and potentially in early detection of the disease.

Additionally, a positive correlation between the expression levels of CYP1A1 and CYP1B1 in NSCLC tumor tissues could enhance their utility as combined biomarkers for lung cancer. Testing for both enzymes might improve the accuracy of lung AC and lung SCC diagnoses. The aryl hydrocarbon receptor (AhR) is a key regulator for both CYP1A1 and CYP1B1. Activation of AhR by environmental toxins leads to the transcriptional activation of these enzymes. Research has shown that AhR overexpression correlates positively with CYP1B1 levels in NSCLC, suggesting that the same signaling pathways may enhance the expression of both enzymes in tumor tissues [14].

The patterns observed both in CYP1A1, and CYP1B1 was mirrored where high-expression groups consistently show lower survival probabilities compared to low-expression groups. This trend suggests a potential role of these enzymes in influencing patient outcomes in cancer contexts. The trends observed in current results regarding CYP1A1 and CYP1B1 expression levels align with existing literature that

suggests these enzymes play significant roles in cancer proliferation and patient survival [15–17]. However, the lack of statistical significance highlights the complexity of their roles and suggests that additional factors may influence outcomes.

The study also explored the association of CYP1A1 and CYP1B1 overexpression with clinical features, aiming to determine distinct clinical implications. The existing literature does not directly address the relationship between clinical features and the expression levels of CYP1A1 and CYP1B1 in AC and SCC of the lung. The current research indicates that there is no significant association between demographic or clinical variables and the expression levels of CYP1A1 and CYP1B1 in lung AC and lung SCC tissues. This finding has two implications. First, the lack of association with demographic and clinical variables suggests that the expression levels of CYP1A1 and CYP1B1 are likely driven by intrinsic factors within the tumor biology itself rather than by external patient characteristics. This points towards genetic or molecular mechanisms within the cancer cells that regulate these enzymes. Second, since CYP1A1 and CYP1B1 expression levels are not significantly influenced by patient demographics or clinical variables, these enzymes could serve as universal biomarkers for lung AC and lung SCC. Their expression can be considered relevant across diverse patient populations, making them broadly applicable for diagnostic purposes. Future research efforts could focus more on understanding the molecular and genetic drivers of CYP1A1 and CYP1B1 expression in lung cancer rather than considering demographic or clinical factors [7, 18]. This could lead to a better understanding of the pathways and processes that regulate these enzymes within the tumor environment.

Although the findings of this research study provide valuable insights into the CYP1A1 and CYP1B1 expression profiles in Turkish lung AC and lung SCC, the study is hampered by two limitations related to sampling and data collection that should be considered. These limitations warrant cautious interpretation of the findings. The first limitation is the sample size, which, while sufficient for an initial analysis, may not adequately represent the associated clinical features. Secondly, the study primarily focuses on immunohistochemical analysis and does not account for the influence of individual genotypic variation on the protein expression profile. This limitation may restrict a comprehensive understanding of how variations in the metabolism pathway of carcinogens contribute to lung cancer in the study population.

Conclusion

The expression profile of CYP1A1 and CYP1B1 enzymes is remarkably elevated in Turkish lung AC and lung SCC, suggesting their potential as decisive biomarkers for risk stratification and early detection.

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Serpil Oğuztüzün: general evaluation of the work, control and critical comments with an intellectual perspective, and evolution of the text to the appropriate level.
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