Original Article

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The Relationship of Sirtuin 1 and Sirtuin 2 Expression with Clinicopathological Parameters in Non-Small-Cell Lung Carcinomas

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Abstract

Aim: Recent studies have shown that sirtuin signaling pathway activation could be a potential therapeutic target for future therapies and biomarkers for predicting prognosis in cancer. We aimed to investigate the association between Sirtuin 1 (SIRT1) and Sirtuin 2 (SIRT2) immunohistochemical (IHC) protein expression in tumors and clinicopathological parameters and survival profiles in non-small cell lung cancer (NSCLC) patients.

Methods: This retrospective observational study reviewed lung resections (lobectomy, segmentectomy, wedge resection, and pneumonectomy) of 186 patients diagnosed with NSCLC (adenocarcinoma, squamous cell carcinoma, and adenosquamous carcinoma). SIRT1 and SIRT2 expression was classified as high and low expression based on the extent and intensity of IHC staining.

Results: When there was advanced disease, a large tumor, and metastasis to lymph nodes, low levels of SIRT1 and SIRT2 expression were found. A positive correlation exists between high SIRT2 expression and longer overall survival. If SIRT1 and SIRT2 were both overexpressed (+/+), longer survival times were observed than in the group in which either of them was low (+/-, -/+, -/-) (p=0.01).

Conclusion: Our research suggests that SIRT1 and SIRT2 may suppress tumor growth in NSCLC and serve as positive prognostic indicators.

Keywords: Lung, non-small-cell carcinoma, Sirtuin 1, Sirtuin 2, prognosis, immunohistochemistry

Introduction

Non-small cell lung carcinoma (NSCLC), which mainly includes squamous cell carcinoma (SCC) and adenocarcinoma (ADC), accounts for approximately 80% of all lung cancer cases (1). Sirtuins (SIRTs) are a class of proteins with nicotinamide adenine dinucleotide (NAD+)-dependent protein deacetylase and/or ADP ribosyltransferase activities (2). SIRTs are involved in the metabolism, genomic stability, cell cycle, cell division, transcriptional editing, and pathogenesis of various diseases, such as metabolic diseases (2,3). SIRTs function as either tumor promoters or suppressors, participating in various processes, such as autophagy, apoptosis, and energy metabolism (2,3). Recent studies have shown that sirtuin signaling pathway activation could be a potential therapeutic target for future therapies and biomarkers for predicting prognosis in cancer.

We hypothesized that the expression of Sirtuin 1 (SIRT1) and Sirtuin 2 (SIRT2) in NSCLC would be associated with other prognostic parameters and survival. We aimed to examine the relationship between SIRT1 and SIRT2 expression levels, clinicopathological parameters, and survival in patients diagnosed with NSCLC. It is our contention that data on SIRT1 and SIRT2 expression

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in NSCLC may be beneficial for both prognostic and therapeutic purposes.

Materials and Methods

Compliance with Ethical Standards

University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital Clinical Research Ethics Committee approval was obtained with the decision dated 22.07.2020 and numbered 2020/514/182/10, and it was supported by the Health Sciences University Scientific Research Projects Unit with the project code number 2020/097. All procedures conformed to the principles of the Declaration of Helsinki (as revised in 2013).

Data Collection

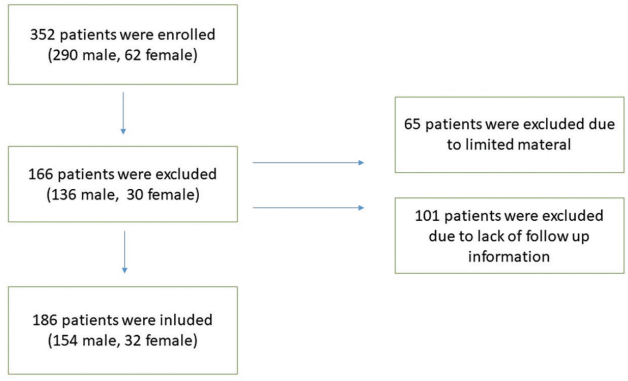
Lung resection (lobectomy, segmentectomy, wedge resection, and pneumonectomy) materials from 186 patients diagnosed with NSCLC (ADC, SCC, adenosquamous carcinoma) diagnosed in our pathology department between 2014 and 2018 were included in the study.

The clinicopathological parameters of the cases were extracted using the hospital automation system, and the clinical staging of the patients was calculated using the 8th Edition TNM classification of the "America Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC)" in NSCLC (4). The age, tumor size, location, histological subtype, number of tumor foci, bronchial involvement, pleural, lymphovascular, and perineural invasion, TNM stages, metastasis/relapse status, and survival data of the patients were recorded. SIRT1 and SIRT2 expressions were investigated immunohistochemically (IHC) and classified as low (low) and high (high) expression.

The inclusion criteria for the study were diagnosis of NSCLC and the presence of sufficient tumor tissue for IHC analysis of SIRT1 and SIRT2 expression. Cases with only needle biopsies and cases with limited material were excluded from the study. In addition, if paraffin blocks belonging to the patient in the pathology archive were absent, if there was a second primary tumor, and/or if the patient's follow-up information required for survival analysis could not be obtained, the case was excluded (Graph 1).

IHC Staining and Assessment

Hematoxylin & Eosin-stained sections of the cases, formalin-fixed and paraffin-embedded blocks, were removed from the archive and examined. A paraffin block that mostly consisted of tumor tissue and normal tissue was selected for each case.



Graph 1. Flow chart of patient selection

IHC staining was performed using "Ventana Medical System-Benchmark Ultra/ISH Staining". The following procedures were performed using the Ultraview Universal DAB Detection Kit: Sections from paraffin blocks were taken on 4-m-thick, positively charged slides. The mixture was kept in an oven at 70 °C for 1 h. The slides were transferred to a Benchmark Ventana Ultra IHC device. Antigen recovery was performed with ethylene diamine tetraacetic acid at pH 8 (CC1). Antibody incubation: SIRT1 (B-7, mouse monoclonal antibody, Santa Cruz Biotechnology, sc-74465, 1/300) and SIRT2 (A-5, mouse monoclonal antibody, Santa Cruz Biotechnology, sc-28298) with a primary antibody duration of 2 hours, 1/100) were applied. Harris Hematoxylin (Ventana Medical Systems) was applied for 16 min for background staining, and bluing reagent (bluing solution) (Ventana Medical Systems) was applied for 4 min. The slides were washed with detergent water, rinsed in absolute alcohol twice, dried, and covered with a xylol-based sealer. Internal and external controls were selected based on the SIRT1 and SIRT2 staining scores of tissues from the Human Protein Atlas (http://www.proteinatlas.org/) (5,6).

Staining scores and SIRT1 and SIRT2 expression levels based on the extent and intensity of staining were calculated using a semiquantitative scoring method, as reported in previous studies (2,7,8). The percentage of positive cells was considered as the extent of staining (0=0, 1=1-25%, 2=26-50%, 3=51-75%, 4=76-100%). The staining intensity was evaluated by comparing it with that of a known external positive control (0, negative; 1, weak; 2, moderate; 3, strong; Figures 1-4). The final IHC score was calculated by multiplying these two values. Based on this score, SIRT1 and SIRT2 expression were classified as high (score >3) and low expression (score ≤3). The cut-off value for the score was obtained by averaging the high and low expressions.

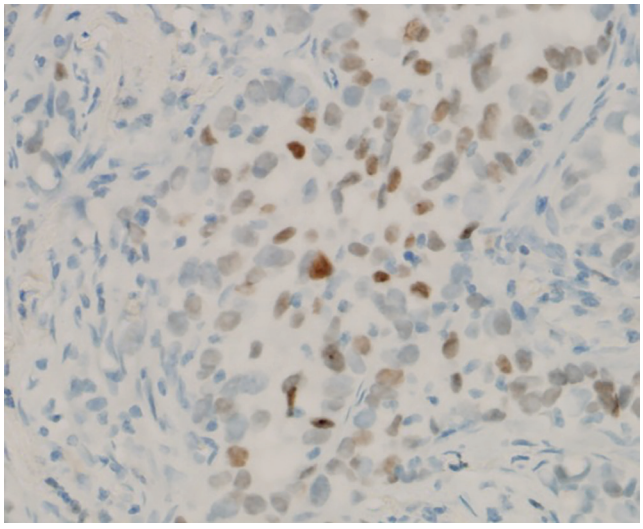


Figure 1. Adenocarcinoma; SIRT1 IHC X400, strong nuclear staining
IHC: Immunohistochemical, SIRT1: Sirtuin 1

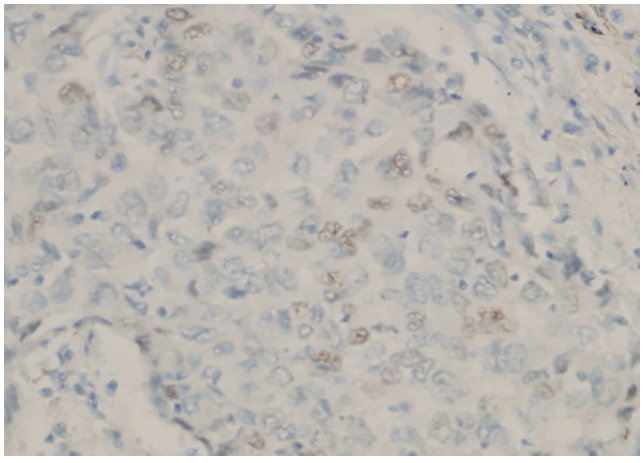


Figure 2. Adenocarcinoma, SIRT1 IHC X400
Adenocarcinoma, SIRT1 IHC X400, moderate staining

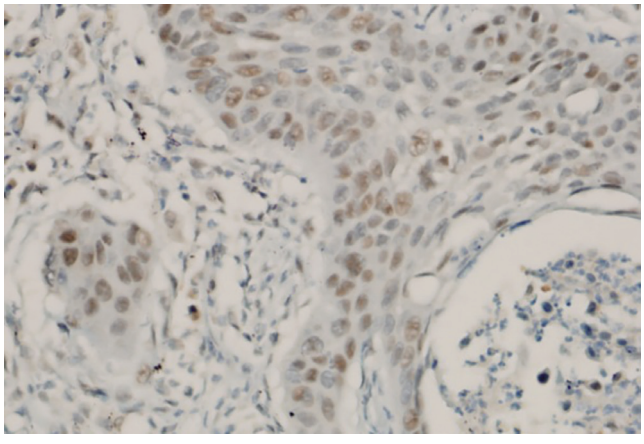


Figure 3. Squamous cell carcinoma, SIRT2 IHC X-400, showing strong staining

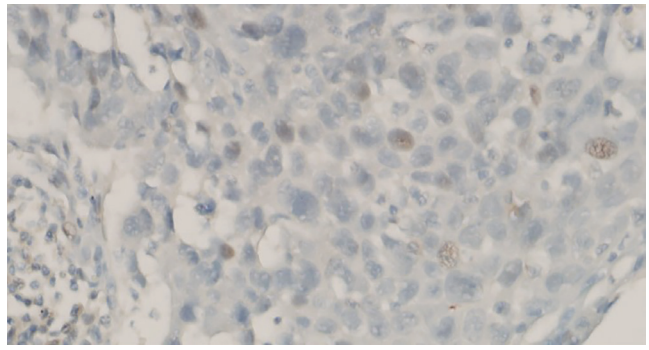


Figure 4. Squamous cell carcinoma, SIRT2 IHC X400
Squamous cell carcinoma, SIRT2 IHC X400, moderate staining

Statistical Analysis

In the data analysis, identifier statistics were presented as frequencies, percentages, averages, and standard deviations. In this study, chi-square (X^2) analysis was used for proportional comparisons of SIRT 1-2 scores according to the characteristics of patients and the Fisher test was performed in the corrections. The independent sample t-test was performed to compare SIRT 1-2 scores with patients' measurements. An independent sample variant analysis was used to examine the difference in patient measurements of SIRT 1-2 compliance ratios. The Sidak test was performed to determine if groups detected differently in the variance analysis. X^2 analysis was applied for proportional comparisons of SIRT 1-2 compliance rates according to the characteristics of the patients, and the Fisher's exact test was performed in the corrections. Progression-free survival and overall survival analyses were performed using the Kaplan-Meier method, and the effects of clinical and pathological features on survival were compared with the log-rank method. In this study, p-values less than 0.05 were considered statistically significant (α=0.05). The SPSS 22.0 package program was used for the statistical analysis.

Results

In the study, 154 (82.8%) of the 186 patients were male and 32 (17.2%) were female. The ages varied between 46 and 80 (average 67.89±8.30). Eighty-seven (46.8%) ADCs, 89 (47.8%) SCCs, and 10 (5.4%) adenosquamous carcinoma cases were included. Metastases were detected in 31.7% of the patients in subsequent clinical follow-ups, of which 24 (40.6%) were in the lung and 13 (22.03%) in the brain. Other rare sites of involvement included the mediastinal lymph nodes, liver, adrenal glands, pleura, and pancreas. The median overall survival was 70 months, with a median disease-free survival of 44 months. Table 1 presents the demographic and clinicopathological features of the patients.

Table 1. Clinicopathological parameters of patients with non-small-cell lung carcinoma			
Parameters		**Number**	**%**
Gender	Male	154	82.8%
	Female	32	17.2%
Pathological diagnosis	Adenocarcinoma	87	46.8%
	Adenosquamous carcinoma	10	5.4%
	Squamous cell carcinoma	89	47.8%
Histologic subtypes of adenocarcinoma	Acinar Solid Lepidic Papillary Micropapillary Could not be evaluated due to artifact detection	44 25 10 5 2 1	23.7% 13.4% 5.4% 2.7% 1.1% 0.05%
Histologic subtypes of squamous cell carcinoma	Keratinized Nonkeratinized Bazaloid	44 42 3	49.43% 47.19% 3.37%
Histologic subtypes of adenosquamous carcinoma	Moderately Mild	7 3	70% 30%
Location	Right upper lobe	58	31.20%
	Left upper lobe	50	26.90%
	Right lower lobe	31	16.70%
	Left lower lobe	20	10.80%
	Left lung	9	4.80%
	Right lung	7	3.80%
	Right middle lobe	6	3.20%
	Lower lobe	1	0.50%
	Rigt lobe	1	0.50%
	Left lower and upper lobe	2	1.1%
	Upper lobe	1	0.50%
Type of surgery	Bilobectomy		3.2%
	Lobectomy	148	79.6%
	Pneumonectomy	28	15.1%
	Segmentectomy	2	1.1%
	Wedge resection	2	1.1%
Vascular invasion	Absent	114	61.3%
	Present	72	38.7%
Perineural invasion	Absent	143	76.9%
	Present	43	23.1%
Bronchial involvement	Absent	133	71.5%
	Present	53	28.5%
Pleural invasion	Absent	141	75.8%
	Present	45	24.2%
Metastasis/Recurrence	Absent	127	68.3%
	Present	59	31.7%
T	T1A	43	23.1%
	T1B	32	17.2%
	T2A	62	33.3%
	T2B	22	11.8%
	T3	27	14.5%

Table 1. Continued			
Parameters		**Number**	**%**
N	N0	131	70.4%
	N1	34	18.3%
	N2	21	11.3%
Stage	1A	60	32.3%
	1B	35	18.8%
	2A	42	22.6%
	2B	26	14.0%
	3A	21	11.3%
	3B	2	1.1%
Survival	Dead Alive	79 107	42.5% 57.5%

Correlations of SIRT1 and SIRT2 with Clinicopathological Parameters

Low levels of SIRT1 and SIRT2 were present in 81.7% (n=152) and 76.9% (n=143) of patients, respectively, while high levels were observed in 18.3% (n=34) and 23.1% (n=43), respectively (Figures 1-4). No significant differences were observed between SIRT1 and SIRT2 expression and histological types of vascular, perinural, and pleural invasion. As presented in Table 2, patients with bronchial involvement had lower SIRT1 and SIRT2 expression than those without bronchial involvement (p=0.03, p=0.04). In the metastasizing/recurring patient group, the SIRT1 and SIRT2 scores also remained lower compared with the non-metastasized group (p = 0.01 and p=0.02, respectively).

The study demonstrated notable variations in the levels of SIRT1 scores across the various N groups; N2 patients exhibited a higher proportion of low SIRT1 expression scores (p=0.04). Conversely, no significant difference was observed in SIRT2 scores across the N levels (p=0.19).

Compared with the cases in the other stages, patients in stage 1A showed higher SIRT1 expression (p=0.01), whereas patients in stages 1A and 1B showed higher SIRT2 expression (p=0.01). Regarding the patients who received neoadjuvant treatment, statistically more patients had lower SIRT1 and SIRT2 scores than those who did not receive neoadjuvant treatment (p=0.04, p=0.04).

The tumor diameters of patients with low SIRT1 and SIRT2 expression were found to be larger, with a statistically significant difference for only SIRT1 (p=0.04).

Regarding overall survival, although a numerically longer survival was found in those with a high SIRT1 score (median 55 vs. 51 months), this difference did not reach statistical significance (p=0.706). When the relationship between SIRT2 score and survival was examined, lower survival times were found in cases with low expression (median 62 versus 47 months), and this difference was statistically significant (p=0.000). Regarding the overall survival times according to histological subtypes, high SIRT2 expression was significantly associated with high survival in the ADC and SCC groups (p=0.025, 0.019, respectively) (Table 3). However, the disease-free survival period showed no significant correlation between SIRT1 and SIRT2 scores (p=0.277).

Regarding age, patients showing high levels of expression for SIRT1/SIRT2 (+/+) were older than those with low expression (-/+, +/-, -/-) (p=0.01). Compared with the second group, the tumor sizes were smaller (p=0.03) and life expectancies were longer (p=0.01) in the older group. Additionally, bronchial invasion rates and metastasis/recurrence states were lower in the "+/+" group than in the other groups (p=0.04, p=0.03). In addition, the "+/+" group had higher T1B levels than the other T levels.

Discussion

The sirtuin family of lysine deacetylase comprises seven members in humans and has been subject to evolutionary conservation. Its role in regulating a multitude of physiological and pathological processes, including aging, cancer, inflammation, and metabolism, is of significant importance (9-13). Sirtuins are involved in a number of significant biological processes, including aging, stress response, vitality, differentiation, metabolism, apoptosis, and cell survival, due to their catalytic activities. However, the mechanisms of action of sirtuin remain incompletely understood because of their dual roles as both tumor promoters and suppressors in different tumors (2,9-14).

SIRT1 and its Effect on NSCLC

A review of the literature revealed conflicting findings regarding the existence of differences in the histologic

Table 2. Correlations of SIRT1 and SIRT2 with clinicopathological parameters

Parameters		SIRT1 EXPRESSION				SIRT2 EXPRESSION				P (SIRT1)	P (SIRT2)
		High		Low		High		Low			
		Number	%	Number	%	Number	%	Number	%		
Gender	Male	31	20.1%	123	79.9%	35	22.7%	119	77.3%	0.01*	0.32
	Female	3	9.4%	29	90.6%	8	25.0%	24	75.0%		
Bronchial involvement	Absent	29	21.8%	104	78.2%	35	26.3%	98	73.7%	0.03*	0.04*
	Present	5	9.4%	48	90.6%	8	15.1%	45	84.9%		
Metastasis/ Recurrence	Absent	27	21.3%	100	78.7%	33	26.0%	94	74.0%	0.01*	0.02*
	Present	7	11.9%	52	88.1%	10	16.9%	49	83.1%		
Neoadjuvant therapy	Absent	33	19.1%	140	80.9%	41	23.7%	132	76.3%	0.04*	0.04*
	Present	1	8.3%	11	91.7%	1	8.3%	11	91.7%		
N	N0	26	19.8%	105		32		99		0.04*	0.19
	N1	7	20.6%	27		7		27			
	N2	1	4.8%	20		4		17			
Stage	1A	18	30.0%	42	70.0%	18	30.0%	42	70.0%	0.01*	0.01*
	1B	3	8.6%	32	91.4%	9	25.7%	26	74.3%		
	2A	6	14.3%	36	85.7%	7	16.7%	35	83.3%		
	2B	4	15.4%	22	84.6%	5	19.2%	21	80.8%		
	3A	1	4.8%	20	95.2%	4	19.0%	17	81.0%		
	3B	2	100.0%	0	0.0%	0	0.0%	2	100.0%		
Tumor diameter (cm)		3.05±2.1		3.77±2.14		3.34±1.96		3.73±2.2		0.04*	0.09

*Significant correlation at the $p<0.05$. X^2: Chi-square analysis was used for proportional comparisons of SIRT 1-2 scores according to the characteristics of patients, and the Fisher's exact test was performed in the corrections.

Table 3. The relationship between SIRT 1 and SIRT2 and overall survival according to pathological diagnosis

Pathological diagnosis	SIRT1 EXPRESSION		SIRT2 EXPRESSION		P (SIRT1)	P (SIRT2)
	High	Low	High	Low		
	mOS (95% CI) (month)	mOS (95% CI) (month)	mOS (95% CI) (month)	mOS (95% CI) (month)		
Adenocarcinoma	55 (46-64)	46 (42-50)	61 (54-68)	45 (39-51)	0.706	0.025*
Adenosquamous carcinoma	65 (-/-)	39 (15-63)	65 (23-107)	35 (14-56)	0.919	0.322
Squamous cell carcinoma	51 (38-64)	57 (50-64)	65 (53-77)	53 (46-60)	0.339	0.019*

*mOS: median overall survival, CI: confidence interval
Overall survival was analyzed using the Kaplan-Meier method, and the effects of clinical and pathological features on survival were compared using the log-rank method

types of NSCLC. Some studies have reported higher SIRT1 expression in ADCs than in SHCs (15,16). Nevertheless, some studies have not identified a significant correlation between sirtuin expression levels and histologic types (16,17). In our series, although no significant difference in SIRT1 expression levels was observed between the ADC and SHC groups, it is noteworthy that SIRT1 expression was higher in the ADC group.

Noh et al. (17) and Gharabaghi (18) reported a correlation between elevated SIRT1 expression and increased tumor size, lymph node metastasis, and tumor stage. Gong et al. (15) reported that high SIRT1 expression is associated with low T stages. In our study, SIRT1 expression was lower in patients with a large tumor size, advanced tumor stage, and N2 lymph node metastasis. The presence of bronchial invasion, which is an important prognostic marker, and SIRT1 expression status were also evaluated. The results demonstrated that SIRT1 expression was lower in patients with bronchial invasion than in those without it. These findings support the hypothesis that SIRT1 acts as a potential tumor suppressor in NSCLC.

In a study by Gong et al. (15), the relationship between SIRT1 and distant metastasis was investigated, and it was found that patients with metastasis exhibited

high SIRT1 expression. In our study, low SIRT1 expression levels were observed in patients with metastasis, whereas high expression was identified as a favorable prognostic parameter.

In studies examining the correlation between sirtuin expression levels and survival, Lee et al. (19) observed a decline in survival rates as SIRT1 expression levels increased. A meta-analysis by Chen et al. (20) included seven eligible studies from diverse geographical locations, encompassing a larger patient cohort. In four studies, a negative correlation was observed between SIRT1 expression and survival (20). Nevertheless, three studies reported no correlation between SIRT1 expression and survival (20). In our study, although subjects with higher SIRT1 expression levels had a numerically longer survival, this difference did not reach statistical significance (p=0.706).

SIRT2 and its Effect on NSCLC

In the study by Gao et al. (21) investigating the protein expression and prognostic value of SIRT2 in patients with nonmetastatic NSCLC, no association was found between SIRT2 and clinicopathologic parameters, such as TNM stage and histologic type. However, survival time was found to be decreased in patients with high SIRT2 expression levels (21). In our study, high SIRT2 expression was observed in early-TNM stage tumors as well as in cases without bronchial invasion or metastasis. Our findings support the hypothesis that SIRT2 acts as a tumor suppressor.

In our study, the overall survival rate was significantly lower in patients with lower SIRT2 expression levels (median 62 months versus 47 months, p=0.000). Li et al. (22) observed significantly lower SIRT2 and higher Skp2 levels in NSCLC samples compared with normal tissue. In this study, a similar result was observed to that of our series, in which patients with NSCLC and low SIRT2 levels exhibited significantly shorter overall survival (22).

Upon examination of the correlation between SIRT2 expression and survival rates across histologic subtypes, patients with high SIRT2 expression exhibited prolonged survival times. The observed difference was statistically significant in the ADC and SHC groups (p<0.05), but not in the adenosquamous carcinoma patient groups (p=0.322).

A comprehensive meta-analysis was conducted by Gong et al. (15) to investigate the clinical significance and potential molecular mechanisms of all sirtuins in lung cancer. The study revealed that patients exhibiting elevated levels of SIRT1 and/or SIRT2 demonstrated markedly diminished disease-free and overall survival compared with patients with diminished levels of at least one sirtuin. In this study, we created SIRT1 and SIRT2 combinations and examined their concordance. We found that cases with high expression for both markers had smaller tumor sizes, lower T stages, and lower progression/recurrence rates compared with other groups. Furthermore, survival times were higher in the SIRT1+/SIRT2+ group than in the other groups. These findings were statistically significant (p=0.01). A review of the literature revealed a paucity of studies in which SIRT1 and SIRT2 protein levels were evaluated in combination and used as measures of disease-free survival. In this regard, our study makes a contribution to the existing literature and provides an illustration of the distinction in the mechanism of action of sirtuin. Our findings are consistent with those of previous studies, indicating that the combined use of both is a more significant prognostic marker. However, in contrast to the literature, we observed that cases with high expression exhibited a superior prognosis.

Study Limitations

It should be noted, however, that the analysis was not without limitations. First, the planned analyses in the ADC and SCC subgroups could not be performed. Second, patients lacking sufficient clinical knowledge and follow-up were excluded from the study, resulting in a reduction in the sample size. The absence of data on treatment modalities and the prevalence of comorbidities also diminished the statistical power of our study. In addition, the present study employed only IHC and used retrospectively available tissue samples obtained from paraffin blocks. Use of multiple methods, such as gene expression measured via qPCR or RT-PCR, protein content measured via Western blotting, blood enzyme levels measured via ELISA, and fluorometric or sirtuin activity assays (23) enhance the reliability of the results. Despite the aforementioned limitations, this study represents one of the few investigations in which SIRT1 and SIRT2 are evaluated collectively, with the objective of identifying a correlation between the clinical values of patients with NSCLC and this approach, which lends a distinctive value to our work.

Conclusion

Our study provides evidence supporting the hypothesis that high SIRT1 and SIRT2 levels may act as tumor suppressors in NSCLC. It can be used as a positive prognostic marker in the context of therapeutic planning for NSCLC. Further research is required to confirm these findings. Well-designed prospective studies with larger cohorts and more comprehensive clinical data are necessary to advance this field of study. The application of supplementary techniques to reinforce and corroborate the IHC approach may be advantageous for the assessment of expression levels.

Ethics

Ethics Committee Approval: Local ethics committee approval was obtained with the decision dated 22.07.2020 and numbered 2020/514/182/10, and it was supported by the University of Health Sciences Turkey, Scientific Research Projects Unit with the project code number 2020/097.

Informed Consent: This is a retrospective observational study.

Footnotes

Authorship Contributions

Concept: F.C.K., N.B.O., S.S., C.C.B., Design: F.C.K., N.B.O., S.S., C.C.B., Data Collection or Processing: F.C.K., N.B.O., Analysis or Interpretation: F.C.K., N.B.O., S.S., C.C.B., Literature Search: F.C.K., S.S., Writing: F.C.K., N.B.O., S.S., C.C.B.

Conflict of Interest: No conflicts of interest were declared by the authors.

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