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Original Research Article

Immunohistochemical Evaluation of p53 and E-Cadherin Expression in Oral Squamous Cell Carcinoma: A Prospective Hospital-Based Study

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Abstract:

Background: Oral squamous cell carcinoma (OSCC) comprises 90% of oral malignancies, with a 5-year survival rate of 50%-60%. p53 and E-cadherin play critical roles in OSCC pathogenesis. Aberrant p53 expression is linked to aggressive tumor behavior and reduced survival rates. Reduced E-cadherin expression promotes tumor invasion and metastasis. Immunohistochemistry allows assessing their expression patterns, providing valuable insights into OSCC development and progression. This study aims to investigate p53 and E-cadherin immunohistochemical expression in OSCC patients, correlating these biomarkers with clinicopathological parameters to explore their prognostic significance and therapeutic potential.

Methods: This prospective immunohistochemical study was conducted on 71 oral squamous cell carcinoma (OSCC) patients diagnosed between August 2021 and July 2022. Tissue specimens were carefully selected to ensure adequate tumor representation and absence of artifacts. Immunohistochemical staining was performed using specific antibodies against p53 and E-cadherin. Scoring systems were used to evaluate the staining intensity and percentage of positively stained tumor cells for both biomarkers. Statistical analysis was conducted to assess correlations between p53 and E-cadherin expression levels and OSCC histopathological grade using ANOVA test ($p < 0.05$). Two independent pathologists blindly evaluated the staining results.

Results: This prospective study included 71 oral squamous cell carcinoma (OSCC) patients. Most were male (74.6%), with a mean age of 55.62 ± 16.29 years. OSCC was commonly found in the buccal mucosa (45.1%) and tongue (25.4%). Histopathological grading revealed 36.6% well-differentiated, 39.5% moderately differentiated, and 23.9% poorly differentiated cases. P53 and E-cadherin expression levels varied significantly based on OSCC grade, with higher p53 expression in poorly differentiated OSCC and lower E-cadherin expression in poorly and moderately differentiated OSCC. Statistical analysis confirmed these associations ($p<0.001$).

Conclusion: Our immunohistochemical study provides valuable insights into the expression patterns of p53 and E-cadherin in OSCC and their potential implications in tumor differentiation and behavior. The significant associations observed between p53 and E-cadherin expression levels and histopathological grade underscore their potential roles as prognostic markers in OSCC.

Keywords: Oral squamous cell carcinoma (OSCC), p53, E-cadherin, Histopathological grade, Prognostic marker

Introduction

Oral squamous cell carcinoma (OSCC) accounts for approximately 90% of all oral malignancies, making it a major public health concern [1]. Despite advancements in medical and surgical treatments, the 5-year survival rate for OSCC patients remains relatively low, hovering around 50% to 60% [2,3].

This alarming statistic underscores the urgent need for a more profound comprehension of the underlying molecular mechanisms driving OSCC pathogenesis and progression [4].

Among the various biomarkers implicated in cancer development, the tumor suppressor gene p53 and the cell adhesion molecule E-cadherin have

emerged as crucial players in several malignancies, including OSCC [5,6].

p53 is a pivotal tumor suppressor protein that plays a central role in regulating cell cycle progression, DNA repair, and apoptosis [7]. Mutations in the p53 gene are frequently observed in numerous cancers, leading to its functional inactivation and consequent loss of cell cycle control and genomic stability [8]. In OSCC, aberrant p53 expression has been linked to aggressive tumor behavior, increased metastatic potential, and decreased patient survival rates, making it an essential biomarker for prognostic evaluation and targeted therapeutic strategies [9].

Conversely, E-cadherin is a transmembrane glycoprotein responsible for maintaining cell-cell adhesion and tissue integrity [10]. In normal tissues, E-cadherin serves as a crucial mediator of cell polarity and differentiation, preventing uncontrolled cell migration and invasion. However, the downregulation or loss of E-cadherin expression, frequently observed in cancer, promotes epithelial-to-mesenchymal transition (EMT) and facilitates cancer cell dissemination, invasion, and metastasis. In OSCC, reduced E-cadherin expression has been associated with advanced tumor stages and a poor prognosis, highlighting its significance as a potential diagnostic and therapeutic target [11].

Given the crucial roles of p53 and E-cadherin in OSCC pathogenesis, their evaluation using immunohistochemical techniques presents an invaluable opportunity to gain insights into the molecular alterations within the tumor microenvironment. Immunohistochemistry offers the advantage of analyzing protein expression patterns within the tumor tissue, thereby providing valuable information regarding the functional status of these biomarkers in the context of OSCC development and progression [8,9,11].

Therefore, the aim of this study is to comprehensively investigate the immunohistochemical expression of p53 and E-cadherin in a cohort of OSCC patients. By correlating the expression levels of these biomarkers with clinicopathological parameters, we aim to elucidate their potential prognostic significance and shed light on their involvement in OSCC tumorigenesis. Furthermore, a better understanding of the interplay between p53 and E-cadherin may uncover novel therapeutic avenues for the management of OSCC, ultimately improving patient outcomes and quality of life.

Materials and Methods

Study Design and Patient Cohort

This prospective immunohistochemical study was conducted on patients diagnosed with oral squamous cell carcinoma (OSCC) between August 2021 to July 2022. The patient cohort was selected from the tertiary care hospital under the department of Pathology, and all cases were confirmed and classified based on histopathological evaluation according to the Anneroth's multifactorial grading approach for OSCC. Ethical approval for this study was obtained from the institutional ethical committee.

Tissue Sample Selection

A total of 71 OSCC tissue specimens were included in the study. Selection criteria ensured that all samples had sufficient tumor representation and were free from necrotic areas or artifacts that could compromise the immunohistochemical analysis.

Immunohistochemistry Staining

Immunohistochemical staining was performed on 4-µm thick tissue sections obtained from each formalin-fixed, paraffin-embedded tissue block. Briefly, sections were deparaffinized, rehydrated, and subjected to antigen retrieval using heat-induced epitope retrieval (HIER). Endogenous peroxidase activity was blocked using 3% hydrogen peroxide in methanol, and non-specific binding was minimized by incubating sections with 5% normal serum.

Primary antibodies against p53 and E-cadherin were used to assess their expression levels. The specific antibodies and their dilutions were as follows: Anti-p53 [clone DO-7, DAKO A/S, CA, USA)], diluted 1:100, and Anti-E-cadherin [(EP700Y) (Rabbit Monoclonal Primary Antibody, Cell Marque)], diluted 1:200.

Sections were then incubated with the primary antibodies overnight at 4°C. Following incubation, sections were washed with phosphate-buffered saline (PBS) and subsequently incubated with secondary antibody 1 hour at room temperature. After the secondary antibody incubation, the sections were washed again with PBS to remove any unbound secondary antibody.

The visualization of antigen-antibody complexes was achieved using diaminobenzidine (DAB), for enzymatic detection. This resulted in the development of a brown precipitate at the location of the antigen of interest. The reaction was stopped by rinsing the sections with distilled water. The immunohistochemically stained sections were then examined and analyzed under a light microscope.

Scoring and Evaluation of Immunohistochemistry

Two independent pathologists, blinded to the clinical data, evaluated the immunohistochemical staining results. The scoring system used for p53 and E-cadherin expression was as follows:

p53: Nuclear staining intensity was scored as follows: 0 (no staining), 1+ (weak staining), 2+ (moderate staining), and 3+ (strong staining). The percentage of positively stained tumor cells was scored as follows: 0 (no staining), 1+ (1-25% positive cells), 2+ (26-50% positive cells), 3+ (51-75% positive cells), and 4+ (76-100% positive cells). The overall p53 expression score was obtained by multiplying the intensity and percentage scores, resulting in a total score ranging from 0 to 12.

E-cadherin: Membrane staining intensity was scored as follows: 0 (no staining), 1+ (weak staining), 2+ (moderate staining), and 3+ (strong staining). The percentage of positively stained tumor cells was scored as follows: 0 (no staining), 1+ (1-25% positive cells), 2+ (26-50% positive cells), 3+ (51-75% positive cells), and 4+ (76-100% positive cells). The overall E-cadherin expression score was obtained similarly to the p53 scoring system.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0. Correlations between p53 and E-cadherin expression levels and histopathological grade of OSCC were assessed using ANOVA test. The significance level was set at $p < 0.05$.

Ethical Considerations

This study was conducted in compliance with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all patients during initial diagnosis and treatment. Patient identities were kept confidential throughout the study, and data were anonymized before analysis.

Results

Present study consisted of 71 patients with oral squamous cell carcinoma (OSCC), with 53 (74.6%) being male and 18 (25.4%) being female. The mean age of the patients was 55.62 ± 16.29 years. Regarding the distribution of OSCC by site, the majority of cases were found in the buccal mucosa (45.1%), followed by the tongue (25.4%), lower alveolar ridge (8.4%), and floor of the mouth (21.1%). The histopathological grading of OSCC revealed that 26 (36.6%) cases were well-differentiated, 28 (39.5%) were moderately differentiated, and 17 (23.9%) were poorly differentiated. In terms of tumor stage, OSCC cases were distributed as follows: stage 1 (18.3%), stage 2 (21.1%), stage 3 (35.2%), and stage 4 (25.4%). The presence of perineural invasion was observed in 16 (22.5%) cases, while 55 (77.5%) cases showed no evidence of perineural invasion. Regarding lymph node metastasis, 34 (47.9%) patients had positive lymph nodes, while 37 (52.1%) patients did not show evidence of lymph node involvement (Table 1).

Table 1: Demographic and Clinical Characteristics of the OSCC patients (N=71).

Variables	Frequency	%
Gender		
Male	53	74.6
Female	18	25.4
Mean Age (in years)	55.62+16.29	
Site		
Buccal mucosa	32	45.1
Tongue	18	25.4
Lower alveolar ridge	6	8.4
Floor	15	21.1
Anneroth's histological grade		
Well differentiated	26	36.6
Moderately differentiated	28	39.5
Poorly differentiated	17	23.9
Stage		
1	13	18.3
2	15	21.1
3	25	35.2
4	18	25.4
Perineural invasion		
Positive	16	22.5
Negative	55	77.5
Lymph node metastasis		
Yes	34	47.9
No	37	52.1

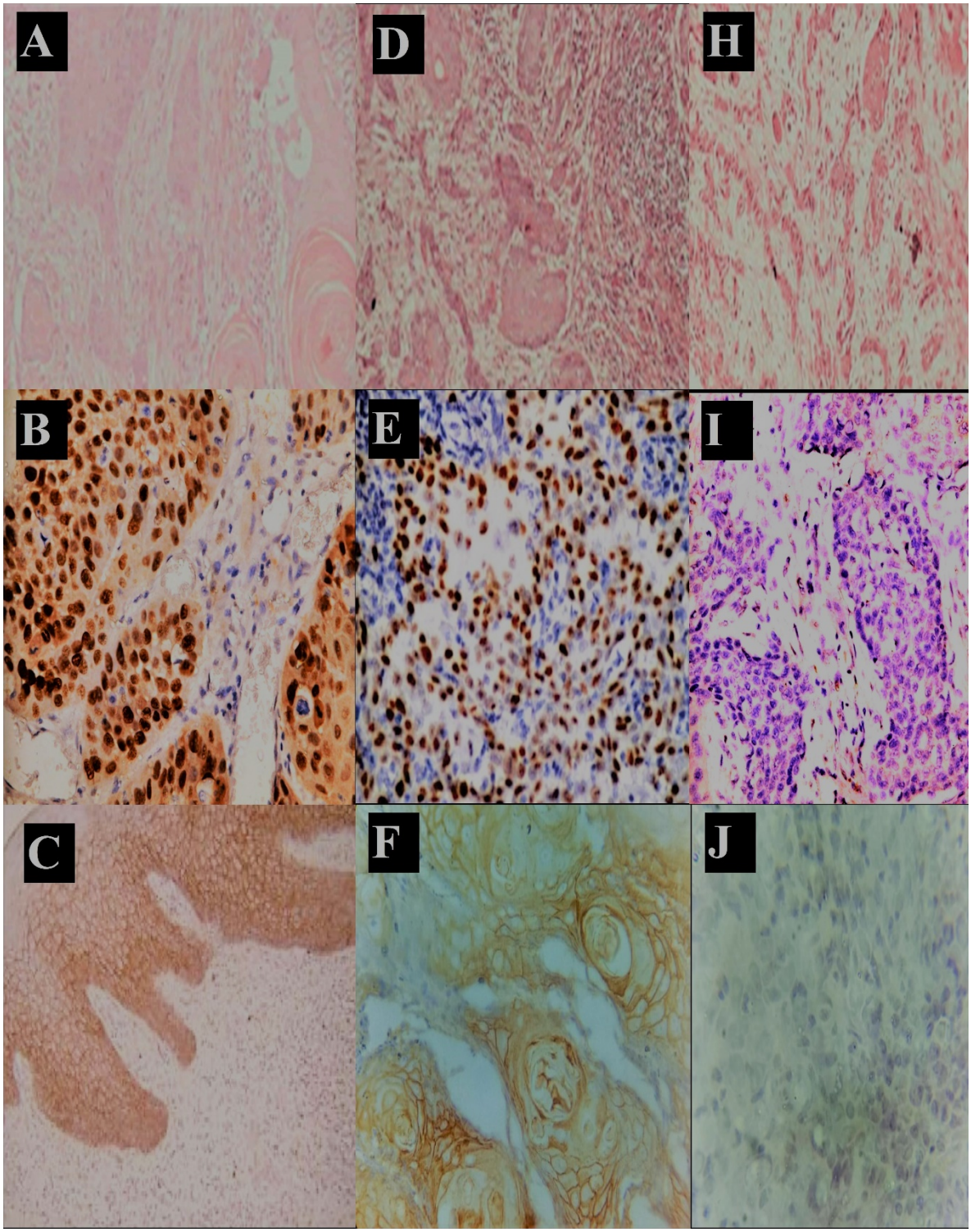

Figure 1: A: Well differentiated OSCC. B: p53 expression in well differentiated OSCC. C: E-Cadherin expression in well differentiated OSCC. D: Moderately differentiated OSCC. E: p53 expression in moderately OSCC. F: E-Cadherin expression in moderrately differentiated OSCC. G: Poorly differentiated OSCC. H: p53 expression in poorly differentiated OSCC. I: E-Cadherin expression in poorly differentiated OSCC

Figure 1. shows that the p53 and E-cadherin expression levels vary significantly based on the histopathological grade of OSCC. The upregulation of p53 and down regulation of E-cadherin are associated with increasing tumor dedifferentiation, suggesting their potential roles as prognostic markers and therapeutic targets in OSCC.

A significant difference in p53 expression was observed among the different histopathological grades of OSCC (F=15.783, df=2, p=0.000). Post hoc

analysis indicated that the mean p53 score was significantly higher in poorly differentiated OSCC compared to well-differentiated (p<0.001) and moderately differentiated OSCC (p<0.001). Additionally, the mean p53 score was significantly higher in moderately differentiated OSCC compared to well-differentiated OSCC (p=0.012). Similarly, there was a significant difference in E-cadherin expression among the different histopathological grades of OSCC (F=24.062, df=2, p=0.000). Post hoc analysis revealed that the mean E-cadherin score was significantly lower in poorly differentiated OSCC compared to well-differentiated (p<0.001) and moderately differentiated OSCC (p<0.001). Moreover, the mean E-cadherin score was significantly lower in moderately differentiated OSCC compared to well-differentiated OSCC (p=0.003)(Table 2).

Table 2: Expression Levels of p53 and E-Cadherin in Different Histopathological Grades of Oral Squamous Cell Carcinoma (OSCC).

Grade	Mean p53 score	Mean E-Cadherin score
Well differentiated (n=26)	23.29±23.18	6.81+2.48
Moderately differentiated (n=28)	41.72±26.63	5.63+1.87
Poorly differentiated (n=17)	71.18±33.74	2.46+1.45
Test of significance	F=15.783, df=2, p=0.000	F=24.062, df=2, p=0.000

Discussion

Oral squamous cell carcinoma (OSCC) is a highly prevalent and aggressive malignancy affecting the oral cavity, with a significant impact on morbidity and mortality worldwide [2]. Despite advancements in medical and surgical therapies, the prognosis for OSCC patients remains relatively poor, necessitating the exploration of novel biomarkers and therapeutic targets to improve patient outcomes [4]. In this prospective immunohistochemical study, we investigated the expression patterns of two crucial biomarkers, p53 and E-cadherin, in a cohort of OSCC patients, aiming to gain insights into their potential roles in OSCC pathogenesis and prognosis.

Present study consisted of 71 patients with oral squamous cell carcinoma (OSCC), with 53 (74.6%) being male and 18 (25.4%) being female. The results aligned with those reported by Dias et al., Pimenta Amaral et al. Kruse et al., and Kazi et al., [12,13,14,15]. In our study, the mean age of the patients was 55.62 ± 16.29 years. The mean age in the studies by Kazi et al., Khandekar et al., Mehrotra et al., and Patelet al., was comparable to our study [15,16,17,18].

The tumor suppressor gene p53 is known for its pivotal role in safeguarding genomic integrity and regulating cell cycle progression, DNA repair, and apoptosis. Mutations in the p53 gene have been reported in various cancers, leading to its functional inactivation and disruption of critical cellular processes. In OSCC, aberrant p53 expression has been associated with aggressive tumor behavior, increased metastatic potential, and reduced patient survival rates [19,20,21].

In our study, the histopathological grading of OSCC revealed that 26 (36.6%) cases were well-differentiated, 28 (39.5%) were moderately differentiated, and 17 (23.9%) were poorly differentiated. Similarly, Dragomir et al., reported 52.9% of cases with well differentiation, 35.3% with moderate differentiation, and 11.8% with poor differentiation in OSCC [22].

In our study the mean p53 score (% of cells stained) in Anneroth grade I (23.29±23.18), grade II (41.72±26.63) and grade III (71.18±33.74) were significantly increasing (p<0.05). In the investigations conducted by Kaur et al., Pandya et al., and Kaur et al., the mean p53 score (percentage of cells stained) showed a significant increase with the progression of Anneroth grade [23,24,25]. Kaur et al., reported that grade I exhibited a mean p53 score of 14, grade II had 78, and grade III showed 100 (p<0.001) [23]. Similarly, Pandya et al., observed mean p53 scores of 42.625 for grade I, 48.888 for grade II, and 70.285 for grade III (p<0.001) [24]. In addition, Kaur et al., found mean p53 scores of 20 for grade I, 72 for grade II, and 88 for grade III (p=0.004) [25]. E-cadherin, a transmembrane glycoprotein, plays a fundamental role in maintaining cell-cell adhesion and tissue integrity. It also functions as a suppressor of epithelial-to-mesenchymal transition (EMT), a process implicated in cancer invasion and metastasis. Downregulation or loss of E-cadherin expression has been linked to increased invasiveness and metastatic potential in various cancers. In our study, the progressive decline of E-cadherin expression in poorly differentiated OSCC suggests its potential involvement in promoting EMT and tumor dissemination in OSCC [26,27].

In our study, there was a significant difference in E-cadherin expression among the different histopathological grades of OSCC (F=24.062, df=2, p=0.000). Post hoc analysis revealed that the mean E-cadherin score was significantly lower in poorly differentiated OSCC compared to well-differentiated (p<0.001) and moderately differentiated OSCC (p<0.001). Moreover, the mean E-cadherin score was significantly lower in moderately differentiated OSCC compared to well-

differentiated OSCC (p=0.003). Similarly studies by Zaid et al., Kaur et al., and Nijkamp et al., showed that decreased E-cadherin expression with increase in histological grades of OSCC.

The correlation between p53 and E-cadherin expression levels observed in this study merits further investigation. It is possible that p53 may regulate E-cadherin expression directly or indirectly through its influence on other regulatory pathways [21,27]. The interplay between p53 and E-cadherin in OSCC pathogenesis warrants in-depth molecular studies to elucidate the underlying mechanisms and identify potential therapeutic targets [20,26].

Our study's strengths include its prospective design and the use of immunohistochemistry to analyze protein expression patterns within the tumor microenvironment. Immunohistochemistry offers valuable insights into the functional status of biomarkers in the context of tumor tissues, providing clinically relevant information for prognosis and targeted therapy. The rigorous evaluation of p53 and E-cadherin expression by two independent pathologists ensures the robustness and reliability of our results.

However, our study has certain limitations that should be acknowledged. The relatively small sample size may restrict the generalizability of our findings. Additionally, the lack of longitudinal follow-up limits our ability to draw definitive conclusions regarding the prognostic significance of p53 and E-cadherin expression in OSCC.

Conclusion

In conclusion, our immunohistochemical study provides valuable insights into the expression patterns of p53 and E-cadherin in OSCC and their potential implications in tumor differentiation and behavior. The significant associations observed between p53 and E-cadherin expression levels and histopathological grade underscore their potential roles as prognostic markers in OSCC. Moreover, our results shed light on the potential interplay between p53 and E-cadherin in OSCC pathogenesis, warranting further molecular investigations.

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