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Original Article

Pathology Section

Histopathological Evaluation of Tumour Infiltrating Lymphocytes in Head and Neck Squamous Cell Carcinoma: A Cross-sectional Study

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ABSTRACT

Introduction: Head and Neck Squamous Cell Carcinoma (HNSCC) is a significant public health concern in India, constituting nearly 30% of all cancer cases. Tumour Infiltrating Lymphocytes (TILs) are an essential component of the tumour microenvironment, influencing tumour progression and limiting tumour invasion, particularly within the tumour stroma. Tumours evade the immune system through the expression of immune checkpoint molecules such as CTLA-4 and PD-L1 on both tumour cells and infiltrating cells. Targeted checkpoint inhibitors can reverse this suppression. HNSCC shows variable prognosis and treatment response. TILs play an important role in the tumour immune response, but their significance in HNSCC is not clearly established. Hence, the present study aimed to evaluate TILs in a cost-effective and routinely used manner in a tertiary care setting.

Aim: To histopathologically evaluate stromal and intratumoural TIL in HNSCC and assess their association with clinicopathological parameters.

Materials and Methods: A retrospective, cross-sectional study was conducted at the Department of Pathology, Ramaiah Medical College, Bengaluru, Karnataka, India, from May 2024 to May 2025. A total of 95 cases of HNSCC were assessed using a standardised method from the International Immuno-Oncology Biomarkers Working group (IBWG). TILs grading for both intratumoural and stromal TILs was given as low (<10%), intermediate (11-50%) and high (>51%). Chi-square tests were used to study the association with prognostic variables like age, gender, tumour site, tumour differentiation, tumour staging, Lymphovascular Invasion (LVI) and Perineural Invasion (PNI) in HNSCC.

Results: Out of 95 cases examined, stromal TILs were low in 62 (65.26%) cases, intermediate in 32 (33.68%) cases and high in 1 (1.05%) case. Intratumoural TILs were high in 45 (47.36%) cases, intermediate in 46 (48.42%) and low in 4 (4.21%) cases. The stromal TILs had a significant association with tumour site (p-value 0.009) and tumour differentiation (p-value <0.001), and the intratumoural TILs had a significant association with tumour differentiation (p-value <0.001) and LVI (p-value 0.036).

Conclusion: The present study demonstrated significant associations with selected clinicopathological parameters and concluded that TILs may serve as a potential prognostic marker. Further longitudinal studies evaluating treatment response and survival outcomes are required. Their evaluation helps in risk stratification and clinical decision-making. TILs' assessment may also identify patients who could benefit from immunotherapy. Routine evaluation of TILs s may contribute to future personalised treatment planning and the development of new therapies.

Keywords: Carcinoma, Histological techniques, Prognosis, Tumour microenvironment

INTRODUCTION

The TILs, derived from both innate and adaptive immune systems, are present in most solid tumours and represent a major component of the tumour microenvironment. Their density and functional state vary widely and play a critical role in tumour progression, immune escape, and response to therapy. Despite shared immunosuppressive pathways, each tumour has a unique tumour microenvironment [1].

The incidence of HNSCC is increasing both globally and in India, accompanied by a declining prognosis. It ranks as the seventh most common cancer worldwide, with approximately 940,000 new cases reported annually [2]. It is a common malignancy of the upper aerodigestive tract and is among the most prevalent cancers globally, accounting for 878,348 new cases and 444,347 deaths in 2020. Despite advances in minimally invasive surgery and treatment de-intensification, HNSCC remains associated with high metastatic potential and poor survival. Current risk stratification relies primarily on clinicopathological factors such as TNM stage and HPV status, while features of the tumour microenvironment are not routinely considered [3,4]. Despite advances in the management of HNSCC, 5-year survival rates remain low, and recurrence is common [5].

TILs have been studied across various malignancies and are shown to add prognostic value beyond the traditional tumour-node-metastasis staging system. While standardised methods for TILs assessment are available for several tumour types, such approaches are largely lacking in HNSCC, and existing studies provide limited evidence regarding their prognostic significance [6,7].

Given the potential of immunotherapy to modulate the tumour microenvironment, targeting immune components may offer improved therapeutic outcomes in head and neck cancers Hence, the present study aimed.

To evaluate TILs and their association with prognostic variables like age, gender, tumour site, tumour differentiation, tumour staging, LVI and PNI in HNSCC to determine their prognostic significance. It explores the relationship between TILs and tumour behaviour, contributes to the limited data on their prognostic value, and highlights their potential role as a biomarker for personalised treatment strategies.

MATERIALS AND METHODS

This was a retrospective cross-sectional study conducted in the Department of Pathology at Ramaiah Medical College, Bengaluru, Karnataka, India, from archived cases of May 2024 to May 2025.

Inclusion criteria: Histopathologically confirmed resected specimens of naïve HNSCC from the oral cavity, nasopharynx and larynx were included.

Exclusion criteria: Small biopsies, non viable/necrotic tissue, and post-treatment resection specimens were excluded from the study.

Sample size determination: From the literature review (Dasgupta S et al., [8]), it was observed that the stromal TILs score was high in 55.6% of the cases. In the present study, expecting similar results with 95% CI, 10% absolute precision, the study requires a minimum of 95 samples.

Study Procedure

For each case, age, gender and location of the lesion were recorded. All specimens were examined by a single pathologist using Haematoxylin and Eosin (H&E) stained sections. Tumours were evaluated for pathological stage, LVI and PNI. Tumours were graded as well-differentiated, moderately-differentiated, or poorly-differentiated according to World Health Organisation (WHO) criteria 2022 [9].

Each slide was initially reviewed at low magnification to identify representative tumour areas, excluding necrotic or degenerated regions. Lymphocytes and plasma cells were assessed exclusively within the tumour cell nests and stroma. Neutrophils, macrophages and dendritic cells were excluded from analysis.

The TILs were categorised as low (<10%), intermediate (11-50%), or high (>51%) as per IBWG [10]. For each slide, five representative fields were evaluated, and the proportion of stromal area occupied by lymphocytes relative to the total stromal area was calculated to derive the final score. The same approach was used to assess intratumoural TILs, and both stromal and intratumoural TILs were recorded for each case [8].

STATISTICAL ANALYSIS

Data was entered into a Microsoft Excel data sheet and was analysed using Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Statistics, Somers, NY, USA). Descriptive statistics of stromal and intratumoural TILs were analysed and summarised in terms of percentage. Chi-square test was used to assess the stromal and intratumoural TILs association with other pathological parameters. A p-value of <0.05 was considered statistically significant.

RESULTS

Of the 95 cases examined, the age of the patients ranged between 46 and 72 years, with a mean of 58.64±12.89 years. Most of the patients belonged to the age group of 51-70 years, 48 cases (50.52%). The majority of the patients were female, 52 cases (54.73%). The most common location of the tumours was in the oral cavity, 90 cases (94.73%). Few tumours, 5 cases (5.26%), were located in the nasopharynx and larynx [Table/Fig-1].

On microscopic examination, 64 (67.36%) cases were found to be moderately-differentiated SCC. Well-differentiated and poorly-differentiated SCC were found in 30 (31.57%) cases and 1 (1.05%) case, respectively. Most of the tumours were in the pathological stage pT2, 36 cases (37.89%). LVI was found to be in 39 cases (41.05%) and PNI in only 14 cases (14.73%). High, intermediate and low stromal TILs were noted in 1 (1.05%), 32 (33.68%) and 62 (65.26%) cases, respectively. Intratumoural TILs were high, intermediate and low in 45 (47.36%), 46 (48.42%) and 4 (4.21%) cases, respectively [Table/Fig-1].

Parameters	Categories	n (%)
Age (years)	31-50	28 (29.47)
	51-70	48 (50.52)
	71-90	19 (20.00)
Gender	Male	43 (45.26)
	Female	52 (54.73)
Site of the tumour	Oral cavity	90 (94.73)
	Others	05 (5.26)
Tumour differentiation	Well	30 (31.57)
	Moderate	64 (67.36)
	Poor	01 (1.05)
Tumour staging	I	7 (7.36)
	II	20 (21.05)
	III	24 (25.26)
	IV	44 (46.31)
pT staging	1	8 (8.42)
	2	36 (37.89)
	3	21 (22.10)
	4	30 (31.57)
pN staging	0	51 (53.68)
	1	13 (13.68)
	2	17 (17.89)
	3	14 (14.73)
LVI	Present	39 (41.05)
	Absent	56 (58.94)
PNI	Present	14 (14.73)
	Absent	81 (85.26)
Stromal TILs	Low	62 (65.26)
	Intermediate	32 (33.68)
	High	1 (1.05)
Intratumoural TILs	Low	4 (4.21)
	Intermediate	46 (48.42)
	High	45 (47.36)

[Table/Fig-1]: Distribution of participants according to the individual parameters.

A statistically significant association was found between stromal TILs and tumour site (p-value 0.009) and also with tumour differentiation (p-value <0.001) [Table/Fig-2].

A statistically significant association was found between intratumoural TILs and tumour differentiation (p-value <0.001)

Variables	n (%)	High TIL n (%)	Intermediate TIL n (%)	Low TIL n (%)	p-value
Age group (in years)					
31-50	28 (29.47%)	21 (75.00%)	7 (25.00%)	0	0.423
51-70	48 (50.52%)	31 (64.58%)	16 (33.33%)	1 (2.08%)	
71-90	19 (20.00%)	10 (52.63%)	9 (47.36%)	0	
Gender					
Male	43 (45.26%)	25 (58.13%)	17 (39.53%)	1 (2.32%)	0.230
Female	52 (54.73%)	37 (71.15%)	15 (28.84%)	0	
Site of the tumour					
Oral cavity	90 (94.73%)	61 (67.77%)	29 (32.22%)	0	0.009*
Other site	5 (5.26%)	1 (20.00%)	3 (60.00%)	1 (20.00%)	
Tumour differentiation					
Well	30 (31.57%)	28 (93.33%)	2 (6.66%)	0	<0.001*
Moderate	64 (67.36%)	33 (51.56%)	30 (46.87%)	1 (1.56%)	
Poor	1 (1.05%)	1 (100%)	0	0	
Tumour staging					

1	7 (7.36%)	4 (57.14%)	2 (28.57%)	1 (14.28%)	0.172
2	20 (21.05%)	13 (65.00%)	7 (35.00%)	0	
3	24 (25.26%)	13 (54.16%)	11 (45.83%)	0	
4	44 (46.31%)	32 (72.72%)	12 (27.27%)	0	
pT staging					
1	8 (8.42%)	4 (50.00%)	3 (37.50%)	1 (12.50%)	0.068
2	36 (37.89%)	23 (63.88%)	13 (36.11%)	0	
3	21 (22.10%)	11 (52.38%)	10 (47.61%)	0	
4	30 (31.57%)	24 (80.00%)	6 (20.00%)	0	
pN staging					
0	51 (53.68%)	35 (68.62%)	15 (29.41%)	1 (1.96%)	0.651
1	13 (13.68%)	6 (46.15%)	7 (53.84%)	0	
2	17 (17.89%)	11 (64.70%)	6 (35.29%)	0	
3	14 (14.73%)	10 (71.42%)	4 (28.57%)	0	
LVI					
Identified	39 (41.05%)	25 (64.10%)	14 (35.89%)	0	0.898
Not identified	56 (58.94%)	37 (66.07%)	18 (32.14%)	1 (1.78%)	
PNI					
Identified	14 (14.73%)	11 (78.57%)	3 (21.42%)	0	0.461
Not identified	81 (85.26%)	51 (62.96%)	29 (35.80%)	1 (1.23%)	

[Table/Fig-2]: Association of Stromal TILs with clinic-pathological parameters.
*Statistically significant

and also with LVI (p-value=0.036) [Table/Fig-3]. Representative photomicrographs illustrating stromal TIL grades are shown in [Table/Fig-4]. Representative photomicrographs illustrating intratumoural TIL grades are shown in [Table/Fig-5].

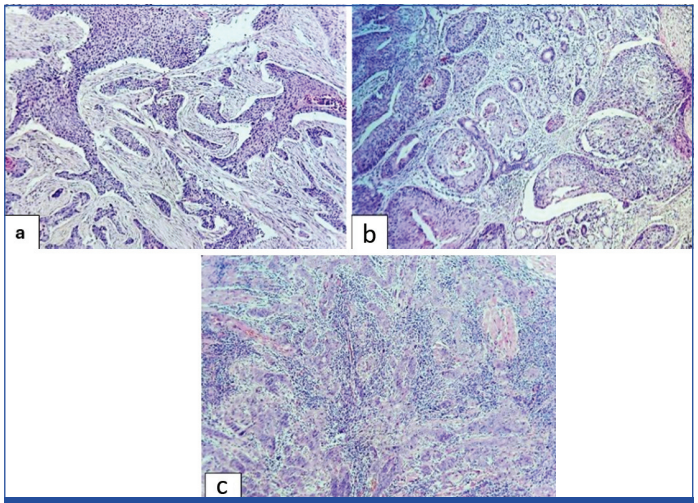
DISCUSSION

Tumour microenvironmental factors, particularly TILs, play a crucial role in the effectiveness of combined cancer treatments such as immunotherapy, chemotherapy, and radiation. Many immune cells within TILs co-exist with cancer cells without attacking them, partly due to immune checkpoint pathways involving PD-1 and PD-L1. Although surgery, radiation, and chemotherapy have been used for decades with limited survival improvement, immunotherapy - especially immune checkpoint inhibitors - has emerged as a highly impactful approach [8,11].

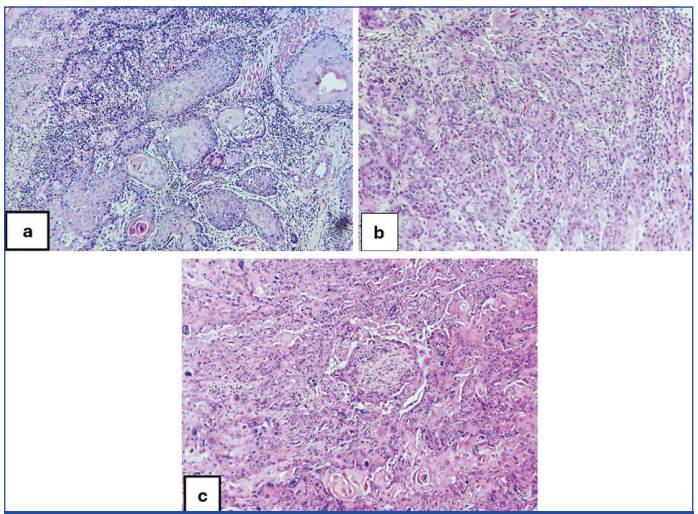
Dasgupta S et al., reported a statistically significant association between stromal TILs and tumour differentiation (p-value=0.005) [8]. Although a higher proportion of cases with elevated stromal TILs was observed in the oral cavity (57.5%), this association was not

Variables	n (%)	High TIL n (%)	Intermediate TIL n (%)	Low TIL n (%)	p-value
Age group (in years)					
31-50	28 (29.47%)	0	16 (57.14%)	12 (42.85%)	0.155
51-70	48 (50.52%)	2 (4.16%)	19 (39.58%)	27 (56.25%)	
71-90	19 (20.00%)	2 (10.52%)	11 (57.89%)	6 (31.60%)	
Gender					
Male	43 (45.26%)	3 (6.97%)	19 (44.18%)	21 (48.83%)	0.823
Female	52 (54.73%)	1 (1.92%)	27 (51.92%)	24 (46.15%)	
Site of the tumour					
Oral cavity	90 (94.73%)	4 (4.44%)	45 (50%)	41 (45.55%)	0.360
Other site	5 (5.26%)	0	1 (20.00%)	4 (80.00%)	
Tumour differentiation					
Well	30 (31.57%)	0	25 (83.33%)	5 (16.66%)	<0.001*
Moderate	64 (67.36%)	4 (6.25%)	21 (32.81%)	39 (60.93%)	
Poor	1 (1.05%)	0	0	1 (100%)	
Tumour staging					
1	7 (7.36%)	0	2 (28.57%)	5 (71.42%)	0.732
2	20 (21.05%)	1 (5.00%)	11 (55.00%)	8 (40.00%)	
3	24 (25.26%)	2 (8.33%)	11 (45.83%)	11 (45.83%)	
4	44 (46.31%)	1 (2.27%)	22 (50%)	21 (47.72%)	
pT staging					
1	8 (8.42%)	0	3 (37.5%)	5 (62.5%)	0.408
2	36 (37.89%)	2 (5.55%)	17 (47.22%)	17 (47.22%)	
3	21 (22.10%)	1 (4.76%)	7 (33.33%)	13 (61.90%)	
4	30 (31.57%)	1 (3.33%)	19 (63.33%)	10 (33.33%)	
pN staging					
0	51 (53.68%)	3 (5.88%)	27 (52.94%)	21 (41.17%)	0.303
1	13 (13.68%)	1 (7.69%)	5 (38.46%)	7 (53.84%)	
2	17 (17.89%)	0	5 (29.41%)	12 (70.58%)	
3	14 (14.73%)	0	8 (57.14%)	6 (42.85%)	
LVI					
Identified	39 (41.05%)	2 (5.12%)	13 (33.33%)	24 (61.53%)	0.036
Not identified	56 (58.94%)	2 (3.57%)	33 (58.92%)	21 (37.50%)	
PNI					
Identified	14 (14.73%)	1 (7.14%)	5 (35.71%)	8 (57.14%)	0.322
Not identified	81 (85.26%)	3 (3.70%)	41 (50.61%)	37 (45.67%)	

[Table/Fig-3]: Association of intratumoural TILs with clinicopathological parameters.
*Statistically significant



[Table/Fig-4]: Stromal TILs: a) Low stromal TILs (H&E, 400X); b) Intermediate stromal TILs (H&E,400X); c) High stromal TILs (H&E, 400X).



[Table/Fig-5]: Intratumoural TILs: a) Low intratumoural TILs (H&E,400X); b) Intermediate intratumoural TILs (H& E,400X); c) High intratumoural TILs (H&E,400X).

statistically significant (p-value 0.126). In contrast, the present study demonstrated a significant association between stromal TILs and tumour site (p-value=0.009). Furthermore, Dasgupta S et al., found that intratumoural TILs were significantly associated with tumour differentiation (p-value=0.002) and LVI (p-value=0.004) [8]. These findings are consistent with the present study, which also showed significant associations for tumour differentiation (p-value <0.001) and LVI (p-value=0.036) [Table/Fig-2,3].

The study by Kunhikoloth S et al., reported similar findings where there was a significant correlation between the stromal TILs and tumour differentiation (p-value <0.001) [Table/Fig-2] [11]. However, there was no significant correlation between the stromal TILs with other parameters such as age, gender, tumour stage, pT, pN stage, LVI and PNI (p-value >0.05), but had high stromal TILs in the advanced stages, suggesting a strong immune response. High percentages of high stromal TILs were seen in stage IV (72.7%), pT4 (80%), pN3 (76.9%), LVI (64.1%) and PNI (78.6%). There was no significant association between the intratumoural TILs and other parameters such as age, gender, tumour site, tumour stage, pT, pN and PNI, but most of them had intermediate intratumoural TILs in the advanced stages. This response may not be as strong as seen with the stroma, but there is an immune response. Intermediate grade of intratumoural TILs was seen in stage IV (50%), pT4 (63.4%) and pN3 (57.1%) [Table/Fig-2,3]. Koukourakis IM et al., in their study, had high TIL density in early T-stage tumours and found no association with N stage, which was similar to the current study, where intratumoural TIL was higher in T3 than in T4 [12]. Similarly, Faraji F et al., demonstrated that including the TILs along with the TNM staging system provides a more accurate prognostic stratification for patients with Human Papillomavirus (HPV)-associated oropharyngeal carcinoma [13]. Kuba K et al., showed that stromal TILs were a good prognostic factor and were found to be more valuable as part of a combined factor compared to intratumoural TILs [14]. In a related study, conducted by Contrera KJ et al., TILs were consistently linked to improved survival in head and neck SCC and showed strong prognostic value across sites [15]. TILs also predict response to therapies - particularly immunotherapy and chemoradiotherapy and are also elevated in responders in neoadjuvant settings.

Suzuki H et al., demonstrated that TILs may serve as a prognostic indicator and biomarker for response to chemoradiotherapy in HNSCC [16]. Their assessment is straightforward and can be performed using routine H&E staining. Their study added that their approach has the potential to significantly enhance the monitoring and reporting of personalised treatment outcomes.

Sukhera ZA et al., suggest TILs as a reliable marker for predicting the presence or absence of cervical nodal metastasis in lip and OSCC [17]. There was a significant association with pN stage and early clinical stage.

Huang Y et al., evaluated the association between TILs, overall survival, and tumour depth in a large, homogeneous cohort of patients with Tongue Squamous Cell Carcinoma (TSCC) [18]. Their findings indicated that low TIL levels were associated with poorer overall survival. In their study, low stromal TILs were more frequently observed in advanced-stage disease (p-value 0.034), which is similar with the current study findings, where change in TIL levels were more common in advanced stages. Additionally, Huang Y et al., reported a significant association between low stromal TILs and PNI (p-value=0.043) [18]. Although a similar trend was observed in the present study, the association did not reach statistical significance (p-value=0.322).

De Ruiter EJ et al., did a systematic review and meta-analysis and confirmed the favourable prognostic impact of TILs in patients with HNSCC [19]. Wolf GT et al., identified that the Worst Pattern of Invasion (WPOI) was significantly associated with low TILs, suggesting that they propose TILs as an important prognostic marker in HNSCCs [20].

Suárez-Sánchez FJ et al., concluded that high TILs is an independent good prognostic factor in OSCC, suggesting their role in antitumour immunity since there was a strong positive association between the TILs and pT and second primary tumours [21].

The H&E staining is routinely used in pathology laboratories worldwide for cancer diagnosis in clinical practice. Shaban M et al., suggests automated approaches for extracting TILs-related information from whole-slide images can support treatment planning by assessing the host immune response [22].

Research on TILs in HNSCC is underexplored when compared to breast cancer and melanoma. Methods for evaluating TILs in HNSCC, particularly using H&E staining, are not yet widely validated. Consequently, more clinical data and studies on large cohorts are required to standardise TILs assessment.

Limitation(s)

The limitations of the current study include the absence of evaluation by relatively expensive immunohistochemical markers such as CD8+ cytotoxic T cells, CD4+ helper T cells, and FoxP3+ regulatory T cells and automated or digital scoring methods. The heterogeneity of tumour sites and variability in HPV status may have influenced the findings. Additionally, observer variability represents a potential source of bias in TILs assessment.

CONCLUSION(S)

Evaluation of TILs on routine H&E stained sections using the standardised criteria from the IBWG is a feasible, cost-effective, fairly reproducible surrogate and clinically practical approach to assess the immune microenvironment in HNSCC. Consistent with recent studies, higher TIL scores on H&E sections are associated with improved prognostic outcomes and may reflect the host antitumour immune response.

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- Manual Googling: Apr 25, 2026
- iThenticate Software: Apr 27, 2026 (3%)

ETYMOLOGY: Author Origin

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AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? No
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

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