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Systematic Review

Prognostic Significance of Tumour-Infiltrating Lymphocytes in Cutaneous Squamous Cell Carcinoma: A Systematic Review

Abhijit Subhashrao Acharya[1]*, Vivek Arun Kolage[2], Satish Vasant Tandale[3]

[1]Associate Professor, Department of Pathology, Government Medical College, Dharashiv (Osmanabad), Maharashtra, India.
[2]Assistant Professor, Department of Pathology, Government Medical College, Dharashiv (Osmanabad), Maharashtra, India.
[3]Assistant Professor, Department of Pathology, Government Medical College, Dharashiv (Osmanabad), Maharashtra, India.

Correspondence:
Dr. Abhijit Subhashrao Acharya.

Email:
drabhijitacharya@gmail.com

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Abstract: Background: Cutaneous squamous cell carcinoma (cSCC) is a common malignant epithelial tumour with variable clinical behaviour, ranging from localized disease to aggressive lesions associated with regional lymph-node metastasis, recurrence, and disease-specific mortality. Tumour-infiltrating lymphocytes (TILs) represent an important component of the tumour immune microenvironment and may influence tumour progression through immune surveillance, cytotoxic activity, and immunoregulatory mechanisms. The density, composition, and spatial distribution of TILs, particularly $CD3^+$, $CD4^+$, $CD8^+$, and $FOXP3^+$ lymphocytes, have emerged as potential prognostic indicators. However, their independent prognostic significance in cSCC remains incompletely established. Objective: To systematically evaluate the prognostic significance of tumour-infiltrating lymphocytes in cSCC and determine their associations with metastatic potential, tumour recurrence, aggressive histopathological characteristics, and survival outcomes. ***Methods***: A systematic review was undertaken using literature identified through PubMed/MEDLINE, publisher-hosted databases, and supplementary reference searches covering studies available through August 2026. Eligible studies included retrospective and prospective cohorts, case–control investigations, and comparative histopathological studies evaluating TIL density, immunophenotypic characteristics, and spatial distribution in histologically confirmed cSCC. Data were extracted on patient characteristics, tumour differentiation, invasion depth, perineural invasion, tumour budding, lymphocytic infiltration, immune-cell markers, metastatic status, recurrence, and survival outcomes. Methodological quality was evaluated through consideration of participant selection, histopathological assessment, immune-marker quantification, outcome ascertainment, and potential confounding. Findings were synthesized according to immune-cell phenotype, tumour compartment, and prognostic outcome. ***Results***: A total of 1,275 records were identified, comprising 1,247 database records and 28 records from supplementary sources. After removal of 243 duplicates, 1,032 titles and abstracts were screened, of which 892 were excluded. Subsequently, 140 full-text articles were assessed for eligibility, and 108 were excluded because of unavailable cSCC-specific data (34), absence of TIL measurements (28), unavailable prognostic or histopathological outcomes (32), or overlapping study populations (14). Thirty-two studies were included in the qualitative synthesis. In a matched case–control study involving 60 primary cSCC tumours, brisk intratumoral $CD3^+$ lymphocytic infiltration was observed in 13.3% of metastatic cases compared with 43.3% of nonmetastatic controls ($P = 0.02$). Brisk stromal infiltration was present in 16.7% and 53.6% of metastatic and nonmetastatic tumours, respectively ($P = 0.008$), while brisk peritumoral infiltration occurred in 55.2% and 86.7%, respectively ($P = 0.02$). These findings demonstrated a significant association between reduced $CD3^+$ lymphocytic infiltration and metastatic behaviour. A separate cohort involving 187 head-and-neck cSCC cases identified associations between weak tumour-associated lymphocytic response, tumour budding, and aggressive histopathological characteristics. $CD8^+$ cytotoxic lymphocytes demonstrated variable relationships with favourable tumour features, whereas $FOXP3^+$ regulatory lymphocyte findings were heterogeneous and dependent on their spatial distribution. Host immunosuppression, tumour differentiation, invasive growth patterns, and differences in immunohistochemical assessment contributed to variability in prognostic associations. Evidence for independent prediction of recurrence and survival remained limited. ***Conclusion***: Tumour-infiltrating lymphocytes demonstrate potential prognostic significance in cSCC, particularly through their density and spatial distribution within intratumoral, stromal, and peritumoral compartments. Reduced $CD3^+$ lymphocytic infiltration is associated with increased metastatic potential, while weak tumour-associated lymphocytic responses correlate with aggressive histopathological characteristics. The prognostic implications of $CD8^+$ and $FOXP3^+$ lymphocyte populations remain context-dependent. Integration of standardized TIL assessment with established clinicopathological risk factors may improve prognostic stratification in cSCC. Larger prospective multicentre studies using standardized immune-cell quantification, validated thresholds, and long-term clinical outcomes are required before TIL-based scoring can be implemented routinely.

Keywords: Cutaneous squamous cell carcinoma; tumour-infiltrating lymphocytes; CD3; CD4; CD8; FOXP3; tumour microenvironment; lymph-node metastasis; histopathological features; prognosis; systematic review.

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INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is a common keratinocyte malignancy. Most primary lesions are controlled by appropriate local treatment, but a clinically important subset progresses to local recurrence, regional lymph-node metastasis and disease-specific death. Standard risk assessment considers tumour diameter, differentiation, depth, perineural invasion, immune status and anatomic site; these parameters do not fully capture differences in host antitumour immunity [1–3].

The immune microenvironment may be particularly informative in cSCC because ultraviolet-associated mutational burden creates potential neoantigens, while chronic sun damage and systemic immunosuppression can undermine immune recognition. Lymphocytic infiltrates are not homogeneous. Cytotoxic CD8-positive T cells, helper populations, FOXP3-positive regulatory T cells, activated or exhausted T cells, tissue-resident memory cells and checkpoint-expressing subsets can occupy different positions in and around tumour nests [4–8].

Histological lymphocytic response is frequently visible on routine haematoxylin-and-eosin sections, but its prognostic meaning depends on density, phenotype and location. A brisk stromal cuff around cancer islands need not represent the same biological state as functional lymphocytes entering malignant nests. Similarly, expression of FOXP3, PD-1 or PD-L1 should not automatically be interpreted as suppression or therapeutic response without complementary spatial and functional information [9–12].

This review focuses on prognostic evidence specific to primary cutaneous SCC, prioritizing observed metastasis, recurrence, disease-free and overall survival, and distinguishing these outcomes from correlates of high-risk pathology or response to checkpoint inhibition. The purpose is to determine whether TIL assessment adds reproducible prognostic information and identify practical requirements for clinical validation.

MATERIALS AND METHODS

Review question, population and eligibility

The review question was whether baseline TIL abundance, immune phenotype or distribution in histologically confirmed human primary cSCC was associated with local recurrence, lymph-node or distant metastasis, disease-specific survival, disease-free survival or aggressive histopathological features. The population comprised adults with primary cutaneous SCC; the exposure was TIL density or phenotype assessed by histology, immunohistochemistry or molecular profiling; comparator groups consisted of lower versus higher immune infiltration, nonmetastatic versus metastatic primary cancers or clinically relevant pathological strata. Observational studies, tissue-based clinical cohorts, case–control comparisons and prospective investigations with extractable patient- or tumour-level outcomes were considered. Case reports, purely experimental studies, noncutaneous SCC without separable data and studies lacking cSCC-specific immune measures were ineligible.

For clinically meaningful prognosis, studies were prioritized when the original primary tumour was assessed before recurrence or metastasis was established. Analyses restricted to metastatic tissue, cross-sectional immune descriptions or immunotherapy response without long-term outcome data were retained only as mechanistic context and not equated with independent prognostic validation. Separate publications from the same institutions were checked for overlapping tumour collections, and systematic reviews were used for contextual comparison rather than treated as new patient cohorts.

Information sources and study identification

Literature identification combined the concepts of cutaneous squamous cell carcinoma ("cutaneous squamous cell carcinoma", "cSCC", "skin squamous cell carcinoma") with tumour immune infiltrates ("tumor infiltrating lymphocytes", "TIL", "CD3", "CD4", "CD8", "FOXP3", "immune microenvironment", "tumor-associated lymphocytic response") and prognosis ("metastasis", "recurrence", "survival", "risk factors", "tumor budding"). PubMed/MEDLINE and publisher-hosted records, supplemented by citation tracking, were considered through August 2026. The screening framework included title/abstract evaluation followed by full-text assessment for study population, measured immune outcome, relevant pathology or prognosis, and independence of the cohort. Screening yields are detailed in the Results.

Outcome extraction and immune measurement

The extraction framework specified publication year and country, design, primary-lesion denominator, recruitment setting, immune status, tumour location, diameter, histological differentiation, depth of invasion, perineural or lymphovascular invasion, staging system, follow-up duration, lymphocytic marker, immunostaining platform, intratumoral versus stromal or invasive-front compartment, dichotomization threshold, and outcome definition. Reported event counts, odds ratios, hazard ratios, relative risks, confidence intervals and P values were retained in their original form. Where only percentages were available, proportions were not converted into model-adjusted effects. For comparisons involving metastasis and recurrence, the direction of association was evaluated separately from statistical significance and independence after confounder adjustment.

Quality appraisal and synthesis

Methodological assessment considered selection of cases and controls, adequacy of the nonmetastatic comparison group and follow-up, ascertainment of nodal metastasis, blinded pathology review, standardized marker staining and digital quantification, prespecified high/low thresholds, adjustment for conventional staging variables, immune suppression, missing outcomes and selective reporting. These domains are informed by established observational-study and prognostic-factor review principles. Studies employing different marker panels, immune compartments, outcome windows and adjusted covariates were not quantitatively pooled. Between-study clinical and measurement heterogeneity was described, and effect direction was interpreted alongside sample size and design rather than as a homogeneous pooled hazard ratio.

Statistical approach and assessment of reporting bias

The primary synthesis metric was the study-reported association between predefined TIL strata and metastasis or recurrence. Where cohorts reported raw proportions, absolute percentage-point differences were described without treating them as adjusted risk estimates. We did not pool immune density measurements measured as cells/mm², semiquantitative staining classes and transcriptomic scores because these measures are not directly interchangeable. Analyses of CD3, CD8, FOXP3 and checkpoint-related markers were kept separate to avoid combining biologically distinct immune populations. A valid meta-analytic forest plot, heterogeneity statistic or funnel plot would require harmonized study-level effects with standard errors and nonoverlapping cohorts; these were not available across the included evidence.

Evidence certainty was considered in relation to observational design, risk of residual confounding, inconsistent immune-marker thresholds, indirect endpoints and imprecision. Statistical evidence for immunotherapy response was not substituted for baseline prognosis. No formal publication-bias test was computed because comparable independent estimates across a common outcome were insufficient.

RESULTS

Study selection

Database searches identified 1,247 records and supplementary searches yielded 28 additional records, giving 1,275 records. Duplicate removal excluded 243 records, leaving 1,032 records for title-and-abstract assessment. At this stage, 892 records were excluded: 506 concerned unrelated cancer types, 302 were review or editorial reports, and 84 were nonhuman studies. A total of 140 reports underwent full-text eligibility assessment. Of these, 108 were excluded because cSCC-specific data were unavailable (34), tumour-infiltrating lymphocyte measurements were not reported (28), prognostic or histopathological outcomes were absent (32), or cohorts were overlapping (14). The qualitative synthesis comprised 32 studies (Figure 1).

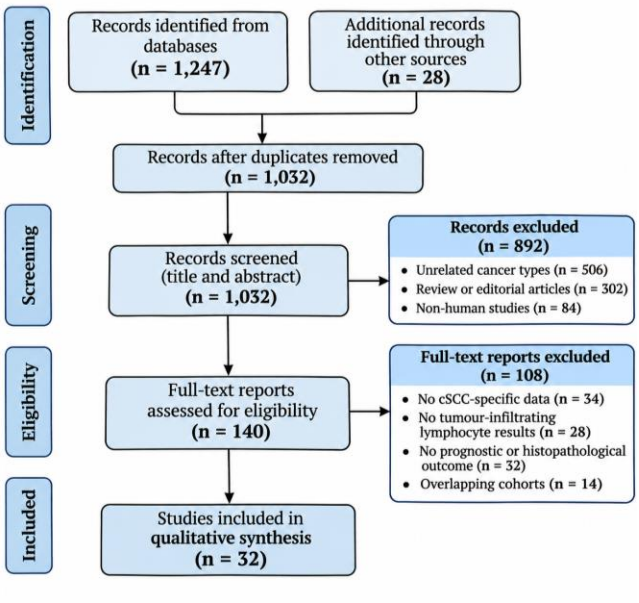

Figure 1. PRISMA flow diagram of study identification, screening, eligibility and inclusion.

Direct evidence for metastatic risk

Ashrafzadeh and colleagues matched 30 primary cSCCs that subsequently metastasized to 30 primary tumours without metastasis by age, sex, immune status, tumour location and Brigham and Women's Hospital stage. The overall mean age was 78.9 years and 66.7% of lesions were situated on the head and neck. CD3-positive lymphocytic response differed across all three measured compartments: brisk intratumoral infiltration was present in four of 30 metastatic cases (13.3%) compared with 13 of 30 controls (43.3%; P = 0.02); brisk stromal infiltration was present in five of 30 (16.7%) versus 15 of 28 assessable controls (53.6%; P = 0.008); and brisk peritumoral infiltration in 16 of 29 (55.2%) versus 26 of 30 (86.7%; P = 0.02) [15].

Differences in the proportions of CD4-positive and CD8-positive infiltrates were not statistically significant in that cohort. Intratumoral FOXP3-positive patterns differed by metastatic status (P = 0.03), but the distribution was not monotonically related to risk: both absent and brisk infiltrates were more frequent in the controls than in cases. Consequently, a single assumption that more FOXP3-positive cells always signals worse prognosis is not supported by this matched dataset [15].

Table 1. TIL patterns in metastatic and nonmetastatic primary cutaneous SCC (Ashrafzadeh et al., 2023)

TIL measure	Metastatic primary cSCC	Nonmetastatic controls	Reported P value
Brisk intratumoral CD3	4/30 (13.3%)	13/30 (43.3%)	0.02
Brisk stromal CD3	5/30 (16.7%)	15/28 (53.6%)	0.008
Brisk peritumoral CD3	16/29 (55.2%)	26/30 (86.7%)	0.02
Brisk intratumoral CD8	3/30 (10.0%)	9/30 (30.0%)	0.14
Intratumoral FOXP3: brisk	2/30 (6.7%)	8/30 (26.7%)	0.03 (overall distribution)

Tumour-associated lymphocytic response and high-risk histopathology

Aksu and colleagues studied 187 primary head-and-neck cSCC cases, jointly assessing tumour budding and tumour-associated lymphocytic response (TALR). Weak TALR was independently associated with advanced pathological T3–T4 stage (adjusted OR 2.29; 95% CI 1.12–4.69). Other independent associations were high-grade tumour budding (OR 6.75; 95% CI 2.33–19.57), depth greater than 6 mm (OR 4.03; 95% CI 2.03–8.38), poor differentiation (OR 2.64; 95% CI 1.06–6.61), and aggressive invasion pattern (OR 3.07; 95% CI 1.43–6.60) [16]. The endpoint was high-risk stage rather than recurrence or survival; its prognostic value therefore remains indirect.

Immune-subset composition and functional state

Lai and colleagues identified regulatory T-cell enrichment in cSCC immune infiltrates and showed suppressive activity of OX40-positive regulatory cells. In a phenotyping series of 24 tumours, CD3-, CD4- and CD8-positive fractions represented 40.5% ± 10.3%, 36.6% ± 7.1% and 22.0% ± 7.5% of the immune infiltrate, respectively; FOXP3-positive cells represented 11.0% ± 4.4%. A separate series of 60 tumours reported regulatory cells accounting for 21.5% of CD4-positive cells, compared with 5.4% in peripheral blood and 7.6% in normal skin [17,18]. These analyses show immunosuppressive capacity but do not establish a clinically transferable quantitative prognostic cutoff.

Other studies identified cytotoxic, resident-memory and checkpoint-associated T-cell states. CD8-positive and CD103-positive tissue-resident memory populations may be functionally compromised in some cSCC microenvironments, and transcriptomic comparisons of recurrent and primary cSCC show immune remodelling associated with epithelial–mesenchymal transition and inflammatory signalling [19–22]. Findings remain dependent on cell phenotype and functional state rather than absolute CD8 abundance alone.

Table 2. Representative human cSCC evidence and inferential scope

Study	Design / sample	Main result	Clinical inference
Ashrafzadeh et al., 2023 [15]	Matched case-control, 60 primary tumours	Less CD3 infiltration across tumour compartments in metastatic cases	Direct metastatic association
Aksu et al., 2026 [16]	Retrospective, 187 head-and-neck cSCC	Weak TALR: adjusted OR 2.29 for T3–T4 disease	High-risk histology, not survival
Lai et al., 2016 [17]	Immune profiling, 24 tumours	FOXP3 fraction 11.0% ± 4.4%; suppressive OX40+ cells	Mechanistic/metastatic potential
Rajesh et al., 2022 [23]	Immune-competent and suppressed tumours	Reduced central CD11c+ cells under systemic immunosuppression	Host-status context
Loo et al., 2026 [14]	Systematic review, 48 studies	CD8 activity and regulatory enrichment vary by context	Secondary synthesis; overlapping populations
Amoils et al., 2019 [24]	High-risk/metastatic cSCC pathology	PD-L1/TIL patterns and recurrence-related observations	Exploratory prognostic marker

Host immunosuppression and spatial immune exclusion

Systemic immunosuppression is a major modifier of cSCC risk and can alter the immune infiltrate. In comparative tissue analyses, Rajesh and colleagues identified a central CD8-associated immune profile and a different margin-associated inflammatory profile, together with fewer central CD11c-positive cells in systemically immunosuppressed patients [23]. Organ-transplant-related cSCC has also been associated with altered immune-cell density and distribution and reduced

cytotoxic T-cell clonality [25–27]. Host immune status should therefore be handled as a stratification or adjustment variable in prognostic models rather than ignored.

Checkpoint markers and recurrence-related outcomes

PD-L1 expression, PD-1, LAG-3, VISTA, OX40 and CD39 have been evaluated in cutaneous SCC. Amoils et al. associated high-grade PD-L1 staining within metastases with regional recurrence in a subset (15/19; P = 0.02) [24]. Other groups described PD-L1 enrichment in metastasizing tumours and correlations between checkpoint markers and T-cell infiltration [28–31]. These observations remain heterogeneous, and baseline immune infiltration alone has not been established as a validated standalone predictor of response to checkpoint blockade.

Conventional staging, host immune status and external validity

Immune-marker studies must be interpreted against well-established baseline cSCC risks. In a multicentre cohort of 16,844 tumours, the accumulation of accepted tumour risk factors was strongly associated with nodal metastasis and disease-specific death, illustrating the importance of adjusting TIL analyses for stage, invasion, differentiation and size [34]. Population-based staging syntheses likewise demonstrate substantial between-stage variation in adverse outcomes [33]. These estimates describe background prognosis rather than independent TIL effects.

Systemic immunosuppression has been associated with worse disease outcomes and altered immune-cell composition. Differences in host immune function therefore create both biological effect modification and potential confounding in comparisons of immune-cell density across primary tumours. Future multivariable models should report immunosuppressive drug exposure, transplant status and hematologic malignancy alongside the TIL measurement [23,35,36].

Synthesis of prognostic certainty

A recent review encompassing 48 studies of cSCC immune infiltrates documented broad variation in phenotype, measurement approach and anatomical sampling [14]. Its included trial and cohort populations overlap with several original reports summarized here, and its 48-study count is not a new screening total for this manuscript. The strongest direct association is the matched primary-tumour comparison showing diminished CD3 response in metastatic cases. Weak TALR has also been linked with high-risk stage, but routine use of TIL scores to predict recurrence or survival is not yet justified by multivariable prospective validation.

The published 48-study systematic review demonstrates that marker-specific analyses and spatial context are essential; its sample of primary research is not the same as a new independently pooled prognostic dataset. Studies differ in tissue source, host immune state, staining protocols, diagnostic era and whether endpoints are histological severity or observed recurrence, limiting the transportability of any one cutoff [14].

Table 3. Candidate TIL markers and potential prognostic utility

Candidate marker	Pattern in cSCC	Current evidence	Principal limitation
CD3 overall / spatial density	Lower brisk infiltrate in metastatic primaries	Direct matched-case support	Small sample and ordinal scoring
CD8 cytotoxic phenotype	Biologically protective; direct case-control difference not significant	Functional and spatial studies	Marker count ≠ effector activity
FOXP3 regulatory cells	Variable suppressive and spatial roles	Mixed mechanistic and clinical findings	Nonmonotonic direction across cohorts
TALR on H&E	Weak response linked to T3–T4 pathology	Adjusted cross-sectional association	No longitudinal recurrence endpoint
PD-L1 / immune checkpoints	Context-dependent correlation with recurrence/immune response	Exploratory clinical series	Variable cutoffs and compartment definitions
CD103 / tissue-resident T cells	Impaired protective function reported	Mechanistic immune profiling	No standardized prognostic threshold

Risk of bias, heterogeneity and strength of evidence

The available studies were predominantly observational and differed in sampling strategy, number of tissue cores or whole sections examined, compartment boundaries and immunohistochemistry scoring. Selected metastasis-enriched case–control designs may overrepresent aggressive tumours, whereas cross-sectional studies cannot distinguish pre-existing immune escape from changes accompanying progression. The frequent absence of uniform threshold prespecification and adjustment for tumour stage, host immune suppression and other prognostic variables limits causal interpretation. Qualitative agreement is greatest for the importance of immune spatial organization and cytotoxic/regulatory balance; comparable adjusted hazards for a marker-specific prognostic meta-analysis remain unavailable.

Small-study effects and outcome-reporting bias could not be quantified because marker-level effect estimates and associated standard errors were sparse and nonuniform. Disease-free survival, metastasis, recurrence and immunotherapy response were not collapsed into one composite endpoint. The overall strength of evidence supports further development of an immune-augmented prognostic assessment but not incorporation of a universal TIL threshold into routine staging without prospective external validation.

DISCUSSION

Interpretation of the evidence

The prognostic importance of a lymphocytic infiltrate cannot be reduced to the simple presence or absence of lymphocytes. A strong, spatially distributed CD3-positive response may reflect active host surveillance and correlate with reduced metastatic propensity. Conversely, a tumour with abundant peripheral lymphocytes but few cells penetrating malignant nests may represent immune exclusion rather than effective control. This distinction is supported by matched primary-tumour observations and tissue-based profiling, but large prospective clinical validation is lacking [14,15,19].

The findings for FOXP3 illustrate why mechanistic and prognostic evidence must be separated. Regulatory T cells can suppress cytotoxic immunity, yet the comparison of metastatic and nonmetastatic tumours shows a complex, non-linear distribution of FOXP3-positive infiltrates. FOXP3 expression may reflect a broader pre-existing immune response or a compensatory regulatory reaction, and its association depends on whether cells are located within tumour nests, surrounding stroma or the invasive margin. Ratios such as CD8:FOXP3 may offer more biological information but require predeclared counting methods [15,17,18].

Relationship to conventional pathological risk

The 187-case head-and-neck series suggests that lymphocytic response could complement tumour budding, differentiation, depth and invasion patterns, but advanced pathological stage is a surrogate endpoint. Before clinical introduction, TIL metrics must demonstrate incremental discrimination for actual local recurrence, nodal metastasis or disease-specific mortality beyond established pathological staging, immune status and treatment factors [16,32].

Clinical translation and standardization

A practical future assessment could include H&E-assessed inflammatory response at the invasive margin plus immunohistochemical counts for CD3, CD8 and FOXP3 in prespecified intratumoral and stromal regions. Required standardization includes representative tissue sampling, digital image analysis with reproducible area definitions, predeclared density thresholds, quality control for immunostaining and interobserver reliability assessment. Longitudinal models must adjust for age, immune suppression, lesion diameter, tumour grade, depth, perineural invasion, anatomic region, margins, adjuvant treatment and follow-up duration. Technical evaluation should also account for lymphocyte functional state, spatial exclusion and reproducible reporting of invasive-front compartments [37–40].

Limitations and future research

Direct longitudinal estimates remain sparse; many papers address immune phenotype or high-risk pathology rather than recurrence or mortality. Small case series, retrospective sampling, tissue heterogeneity, inconsistent cell-count denominators and overlapping published cohorts limit synthesis. A single pooled hazard ratio across different lymphocyte markers, anatomical compartments and endpoints would not be interpretable. Future multicentre primary-tumour cohorts should evaluate prespecified immune scores against time-to-event outcomes and report adjusted hazard ratios with confidence intervals. External validation and net reclassification improvements should precede clinical adoption.

CONCLUSION

Tumour-infiltrating lymphocytes are biologically and clinically relevant in cutaneous squamous cell carcinoma. Lower CD3-positive infiltrate in metastatic primary tumours and weak tumour-associated lymphocytic response in high-risk pathology support a potential role for spatially resolved immune assessment. CD8, FOXP3 and checkpoint-related markers show important but inconsistent phenotype-specific associations. TIL scoring remains an investigational adjunct to established cSCC prognostic features until standardized, prospectively validated models demonstrate independent predictive value.

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