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Tissue-resident memory T-cell expressions and their prognostic role in head and neck squamous cell carcinoma: a systematic review and meta-analysis

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Abstract

Background CD8 + tissue-resident memory T lymphocytes (TRM) are a subset of tumor-infiltrating lymphocytes (TILs) that mediate innate immunity. Clinically, they can prevent tumor development, growth and metastasis and play a potential role in immunosurveillance and long-term immunity in head and neck squamous cell carcinoma (HNSCC).

This systematic review and meta-analysis aimed to assess the prognostic significance of CD8 + TRM cells, identified by key immunophenotypic markers CD103, CD69, and CD49a linked to patient outcomes such as overall survival (OS) in HNSCC and its specified subcategory, OSCC.

Methods PubMed, Scopus, and Web of Science databases were searched systematically to include original research articles comprising cross-sectional, observational, experimental studies, and clinical trials. The characteristics of the studies were recorded for years of publication, research design, cancer types, HPV status, staging, diagnostic assays, immunophenotypic markers, and immune response regulators. Hazard ratios (HR) with confidence intervals (CI) and *p*-values were extracted for observing the association between CD103, CD69, and/or CD49a exhibiting CD8 + cytotoxic T lymphocytes with tissue-resident memory potential. The proportion of CD8 + TRM cells co-expressing CD103, CD69, and/or CD49a was estimated by extracting the actual percentage of expression in TME from graphical presentation of data in included studies.

Results Among the 276 studies, 11 studies were included by reviewing the abstract or title and full-text articles. The findings of these studies demonstrated a strong association between CD8 + TRM cells, characterized by the expression of CD103, CD69, or CD49a and improved OS in patients with HNSCC, and its subtype, OSCC. Notably, similar trends were observed within the included studies relative to oropharyngeal squamous cell carcinomas (OPSCC), another recognized subtype of HNSCC. The pooled HR was 0.49 (95% CI: 0.23–1.02, $p < 0.001$), indicating a potential prognostic benefit of CD8 + TRM cell infiltration in HNSCC and related subtypes of OSCC and OPSCC. However, the overall pooled findings at aggregate cancer incidences were not statistically significant ($p > 0.05$).

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Conclusion Increased infiltration of CD8 + TRM cells expressing CD103, CD69, and/or CD49a is associated with better prognosis and OS in HNSCC and its subtype, OSCC.

Trial Registration This systematic review and meta-analysis were registered in the international database of systematic review protocols at https://www.crd.york.ac.uk/prospero/ under protocol identifier: CRD42024570177.

Keywords Head and neck cancer squamous cell carcinoma, Oral squamous cell carcinoma, Oral cancer, Tissue resident memory, TRM, Meta-analysis, Systematic review, CD8, T lymphocytes

Introduction

Head and neck squamous cell carcinoma (HNSCC) represent a diverse group of cancer subsites, including oral squamous cell carcinomas (OSCC), oropharyngeal squamous cell carcinomas (OPSCC), and squamous cell carcinomas (SCC) of the larynx, and hypopharynx. GLOBOCAN 2020 estimates that HNSCC accounts for a significant global burden of approximately 4.5% of all new cancer cases, with the second highest incidence observed in the Asian population while a 30% increase in new cases of OSCC is expected each year by 2030 [1]. Despite advances in treatment, the prognosis for many patients with HNSCC remains poor, with a five-year survival rate of approximately 60%, heavily dependent on the stage and location of the tumor [2]. Recent studies have highlighted the significance of the heterogeneous tumor microenvironment (TME) in the prognosis and treatment of cancers, particularly targeting tumor-infiltrating lymphocytes (TILs) [3].

CD8 + tissue-resident memory T cells (TRM) or CD8 + memory lymphocytes have been found among TILs that reside in epithelial tissues of the TME and have opened an insight into local, rapid, and effective immune surveillance and innate immune response by TILs [4, 5]. In literature, it has been observed that CD8 + TRM cells downregulate the phenotypic markers CCR7, CX3CR1, and KLRG1. This distinguishes them from circulatory T cells derived from central memory T cells (TCM), which upregulate CCR7 and CD62L [6], and from effector memory T cells (TEM), which upregulate CX3CR1 and KLRG1 [7]. The origins, localization, and function of TRM cells were first discovered in 1981 through a study on immunological memory of Listeria monocytogenes in rodents by parabiosis. The study found that tissue memory cells are descendants of early phase lymphoblasts and continuously replenish T cells from the central lymph or a separate memory cell repository. These memory cells may also arise from the spontaneous extravasation of lymphoblasts [8]. The developmental trajectory and adaptation of CD8 TRM cells to tissue-specific properties and functions can provide insight to compare the phenotype, behavior, and clinical significance of CD8 TRM cells across multiple lineages among TILS and is demonstrated in Fig. 1 [9].

CD8 + TRM cells express specific surface receptors, such as CD103, CD69, and CD49a, that are mutually present or mutually exclusive for the identification, retention, and reactivation of CD8 + TRM cells [10]. These surface receptors were recognized as immunophenotypic markers of CD8 + TRM cells in HNSCC and associated cancer subtypes including OSCC utilizing multiplex immunohistochemistry (MxIHC) approach in previous literature [11].

CD103, an integrin protein complex encoded by the ITGAE gene, forms heterodimeric transmembrane receptor on CD8 + TRM cells. This adhesion molecule binds E-cadherin for retention in epithelial tissues within the TME. The ITGAE (CD103) is activated by "inside-out" autocrine signaling from the cytokine; transforming growth factor-β (TGF-β) and T cell receptors (TCRs), which in turn activate the SMAD and NFAT pathways, upregulating CD103 surface expression [12].

CD49a, another integrin molecule encoded by ITGA1 and known as the very late activation antigen (VLA-1), binds to collagen IV in epithelial tissues within the TME and is usually expressed with CD103 on CD8 + TRM cells. It facilitates the retention of CD8 + TRM cells by expression of CD103 in the TME [13]. CD69, a C-type lectin protein, serves as a typical and specific early activation and proliferation marker in CD8 + TRM cells. It inhibits Kruppel-like factor 2 (KLF2), which downregulates sphingosine-1-phosphate receptor-1 (S1PR1), ensuring the long-term persistence of CD8 + TRM cells by preventing their egress from peripheral tissues. Thus, KLF2 and S1PR1 determine whether CD8 + T cells become recirculating or tissue-resident memory cells [14]. Additionally, CD69 directly triggers transcription factor HIF-1α, inducing hypoxia in TILs and facilitating the activation and differentiation of CD8 + TRM cells in the TME [15]. Though limited, current research has identified CD8 + TRM cells in HNSCC and related cancer subtype OSCC with genetic signatures of CD103, CD69, and CD49a as key surface markers, crucial for developing prognostic predictors and targeted therapies. These immunophenotypic markers identify the CD8 + TRM T-cell lineage and indicate retention and early activation in tumor and stromal tissues [16, 17]. Moreover, a previous meta-analysis was conducted to observe the

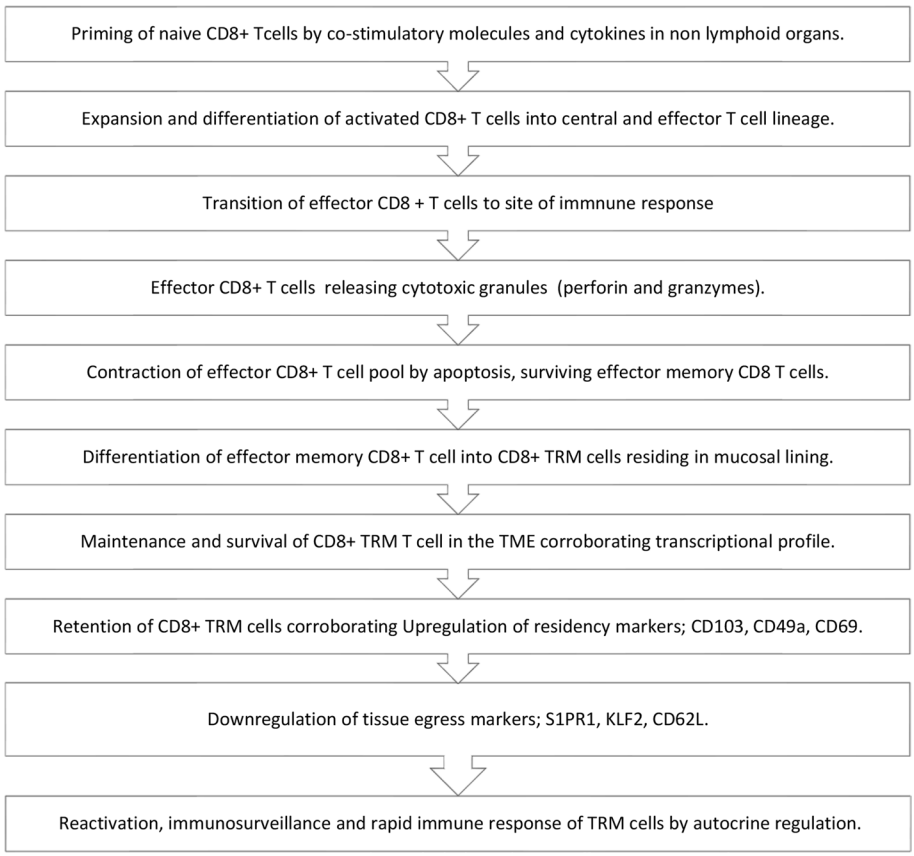

Fig. 1 Transitions from Naive T Cells to CD8 + Tissue-Resident Memory (TRM) Cells [9]

prognostic role of TILs, including CD3+, CD4+, and CD8 + T cells, in HNSCC on the basis of the spatial location of stromal and intra-tumoral tissues and invasive margins [18]. To date, the prognostic role of CD8 + T cell subsets with tissue-resident memory potential in the TME has not been explored in HNSCC and related type of OSCC.

The regulation of CD8 + TRM cells in HNSCC is multifaceted, involving interactions with the TME, immune checkpoints, metabolic factors, and cytokine signaling, as described in Table 1.

Higher expression of fatty acid binding protein 4 and 5 (FABP4/5) on CD8 TRM cells reprograms metabolic pathways utilizing free fatty acids and mitochondrial fatty acids through fatty acid oxidation, thus modulating recruitment and survival in epithelial niches and cytotoxic immune responses. This unique characteristic of CD8 + TRM cells enables them to compete with tumor cells by regulating their metabolic activity, leading to glucose and oxygen deprivation, thereby preventing TRM cell exhaustion [7]. Understanding these regulatory factors can guide the development of therapies aimed at enhancing antitumor activity to play an effective role in head and neck oncology and immunology. Thus, they can display attributes in HNSCC, common to TRM potential residing in TME of the various types of cancers [24] as demonstrated in Table 2.

The variability in the surface expression of CD8 + TRM cells and its relationship to overall survival (OS) necessitates a comprehensive review and meta-analysis to emphasize the significant potential of retention, maintenance, and reactivation of CD8 + TRM cells for prognosis and survival in head and neck oncology. This insight can facilitate the synthesis and consolidation of knowledge on CD8 + TRM cell-specific surface markers, such as CD103, CD69, and CD49a, and their preventive role in tumor growth and recurrence in patients with HNSCC with specific focus on OSCC. To the best of our knowledge, this is the first systematic review and meta-analysis based on the findings of CD8 + TRM T cells expressing immunophenotypes CD103, CD69, and CD49a in HNSCC including specified subcategory OSCC and evaluating their impact on OS. By analyzing the current literature on PubMed (Medline), Scopus, and Web of Science (WOS) databases, this systematic review and

Table 1 The regulation of CD8 + TRM cells in HNSCC and OSCC involving several key mechanisms and Factors

Key mechanisms	Factors	Potential Role
Tissue residency and localization in tumour and stromal epithelial tissues	Adhesion and retention molecules	CD103 binds E-cadherin for retention and regulated by TGF-β and costimulatory TCR on CD8 + TRM cells. CD49a binds collagen IV to increase anchorage of TRM cells and CD69 prevent their tissue egresses in TME [19]
	Chemokines	CXCL9, CXCL10, and CXCL11 bind CXCR3 receptor on TRM cells for migration and retention in TME [20]
Activation and effector functions	Antigen presentation	IFN-γ enhances MHC class I expression, making tumour cells more recognizable to TRM cells, dendritic cells, natural killer cells, B cells and TCM and TEM for their activation and cytolytic function [21]
	Cytokines and Cytotoxic Molecules	Activated CD8 + TRM cells release noncytolytic IFN-γ, TNF-α to stimulate cytolytic GZMB, GNLY and PRF1 [20, 22, 23]
Immune Checkpoint molecules (ICM) and Inhibitory Signals	PD-1) / PD-L1 Pathway:	PD-1 on TRM cells binds PD-L1 on tumour cells, downregulating S1PR1, leading to TRM exhaustion and reduced antitumour activity. ICM inhibitors can rejuvenate TRM cells, enhancing their antitumour response [5]
	Other Checkpoints	Other inhibitory receptors: CTLA-4; TIM-3; TIGIT, and LAG-3 also regulate TRM cell function and their blockade can modulate their activity in head and neck cancer [24]
Inflammatory and Immunosuppressive Factors	Pro-inflammatory Cytokines	IL-15 trans-presentation to CD8 + TRM cells, along with TGF-β, induces clonal expansion and effector release, regulated by T-box transcription factors and essential for long term-survival [25, 26]
Transcriptional regulators		Blim*p*-1 and Hobit (ZNF683) induce and maintain formation of CD8 TRM cells and regulate GZMB [10], Notch regulate CD103 and IFN-γ [11] and RUNX3 regulate TGF-β [12]

Abbreviations: TRM tissue-resident memory T lymphocyte cells, *TGF-β* transforming growth factor- β, *TCRs* T cell receptors, *IFN-γ* Interferon- γ, *TNF-α* tumour necrosis factor-α, *GZMB* granzymes-B, *GNLY* granulysin, *PRF1* perforin, *PD-1* Programmed death-1, *PD-L1* Programmed death-1 ligand, *CTLA-4* cytotoxic T-lymphocyte-associated protein 4, *TIM-3* cell immunoglobulin mucin-3, *TIGIT* T cell immunoreceptor with immunoglobulin and ITIM domain, *LAG-3* lymphocyte activating gene-3, *IL-15* Interleukin-15

Table 2 Heterogeneity in the phenotypic markers of TRM cells across different types of cancers

Cancer types	Immunophenotypic markers of CD8 TRM T cells	References
Head and neck cancer	CD103, CD69, PD-1, Tim-3, LAG-3, CTLA-4	[27]
Oral cancers	CD103, CD69, CD49a, Tim-3, PD-1, CTLA-4	[28]
Oropharyngeal cancer	CD103, CD69, PD-1, CTLA-4, TIM-3, LAG-3, PD-1	[29]
Skin cancers	CD103, CD69, CD49a, CD39, CXCR6	[30]
Lung cancer	CD103 + , CD69 + , CD39 + , LFA-1,	[31, 32]
Cervical cancer	CD103, CD69, CD49a, PD-1, Tim-3	[33]
Esophageal cancer	CD103, CD49a, CD69, CD39, PD-1, CTLA-4	[34]

meta-analysis aimed to assess the prognostic significance of CD8 + TRM cells, identified by key immunophenotypic markers CD103, CD69, and CD49a linked to patient outcomes such as OS in HNSCC and its specified subcategory, OSCC, and explored clinical implications.

Methods

Search strategy

We assessed the existing evidence available in published literature between 01–01-2000 and 20–07-2024. The electronic databases of PubMed (Medline), Scopus, and Web of Science (WOS) were explored for the relevant

studies following methodology described by Dickersin et al. [35].

Search terms

Terms used to retrieve studies were: (head and neck cancer OR oral cancer OR oral tumor OR oral carcinoma OR oral neoplasm) and (squamous cell carcinoma OR HNSCC OR OSCC) and (memory T cell OR memory lymphocytes OR TRM cell) and (tissue resident OR tumor microenvironment). Reference articles were also searched manually. The complete search strategy is demonstrated in Fig. 2.

Selection criteria

Studies included in the systematic review and meta-analysis met the following criteria: (1) patients clinically diagnosed with HNSSC, or its specified subcategory, OSCC, as confirmed by histopathologists evaluation; (2) CD8 + TRM cells expressed with mutually present or exclusive immunophenotypic biomarkers CD103, CD69, and CD49a in the samples of either tumor or stromal tissues of HNSCC, including its subcategory, OSCC, along with other related cancer types; (3) studies reporting the expression of CD8 + TRM cells and survival outcomes in HNSCC and OSCC in terms of hazard ratio (HR) and their related 95% confidence interval (CI); and (4) studies published in the English language. For this study, "related cancer types" refers to studies that analysed CD8 + TRM cell expression in HNSCC without stratifying subsites or that included multiple HNSCC subsites such as OSCC, OPSCC, hypopharyngeal or laryngeal SCC within a pooled analysis. This approach ensured that relevant OSCC data were not excluded when reported within broader HNSCC cohorts.

Studies excluded from the meta-analysis were: (1) duplicated studies retrieved from electronic databases; (2) studies with unavailable full text; (2) studies with no outcome of interest; (3) studies with memory cells obtained from peripheral blood mononuclear cells (PBMCs); (4) studies conducted on mouse models or human xenografts; and (5) studies conducted on TILs other than CD8 TRM cells. If two cohorts were reported in any one study with an independent outcome of interest, they were included as two independent records.

Data extraction

After removing duplicated studies and screening the title/abstract, relevant full-text articles were retrieved and reviewed for inclusion. Pertinent data were extracted from the included studies using a predefined data extraction format. Two independent reviewers performed the data extraction process, and any disparities in the extracted data were resolved through discussion and consensus among all authors of the study. The extraction format captured the potential study characteristics (e.g., author, publication year, study design), participant demographics (e.g., clinical characteristics), intervention details, outcomes of interest (expression of CD103, CD69, CD49a, CD8 + CTL, OS), and any relevant findings related to the intratumoral and mesenchymal stromal cells and tissue-resident memory in head and neck cancers. Data was extracted to assess the methodological quality and risk of bias as part of the synthesis and interpretation of the findings. Regular discussions between the reviewers were conducted throughout the data extraction process to address any uncertainties or discrepancies. We assessed the methodological quality of each study using the Newcastle–Ottawa Scale (NOS), rating three domains: study group comparability (2 stars), participant selection (4 stars), and outcome (3 stars). Studies with NOS ≥ 6 were considered of high quality [36]. This systematic review and meta-analysis was conducted following the REMARK guidelines for reporting tumor biomarkers.

Statistical analysis

Statistical Analysis was performed using STATA statistical software version 17.0 (StataCorp Lp) with hazard ratios (HR) at 95% confidence intervals (CI) from survival data reported within the included studies in systematic review and meta-analysis. We assessed the overall pooled effect, its precision, heterogeneity among studies, and the effect of studies on the overall pooled effect. Variability across the studies was evaluated using I^2 statistics to determine whether a fixed-effect or random-effects model should be used for meta-analysis.

Assuming different true effect sizes and considering sampling errors and heterogeneity among studies, the random-effects model was used for survival analysis ($P < 0.10$, $I^2 > 50\%$) [37]. Egger's test was applied to observe the possibility of publication bias. The "trim and fill" analysis was a statistical method used to adjust for potential publication bias in meta-analysis. The percentage of CD8 + TRM cells expressing CD103, CD69, and CD49a was determined using the Origin Pro software version 2024.

Results

Selection and characteristics of included studies

A total of 276 potential studies were initially retrieved from the electronic databases (Fig. 2).

The duplicates ($n = 88$) were removed by using endnote software version 20 and by manual screening. Abstracts without full-text availability ($n = 2$), studies irrelevant to

head and neck cancers ($n=36$), studies conducted on mouse model ($n=3$), studies lacking relevant outcome of interest on CD8+TRM cells and survival ($n=106$), and non-primary research articles such as reviews and conference proceedings ($n=30$) were excluded after screening. In conclusion, a total of 11 studies were included in this systematic review and meta-analysis to assess the percentage expression of immunophenotypic markers CD103, CD69, and CD49a in relation to CD8+TRM cells, regardless of outcomes of OS in patients with HNSCC and its subsite, OSCC. Of these 11, six potentially relevant studies were selected to evaluate the association between CD8+TRM cell expression and OS.

These six studies comprised three focused on OSCC, one targeting two distinct cohorts for HNSCC, and two studies with three separate cohorts for OPSCC. Additionally, studies reporting data from more than one cohort, each with its respective HR and 95% CI, were treated as separate individual studies and included in the analysis accordingly. Conclusively, statistical analysis was conducted on eight studies ($n=8$) in the meta-analysis, published between 2017 and 2024. HRs and their 95% CI were extracted from all eight studies.

The geographical variation among the study population was observed in China, USA, Germany, Japan, Switzerland, Australia, England, Netherlands, and Singapore, as demonstrated in Fig. 3.

The data on the proportion of CD8+TRM cells expressing immunophenotypic markers: CD103, CD69, and CD49a mutually inclusive or exclusive in TME of various cancer types comparable to HNSCC and OSCC were extracted from the included studies. Numerical values were obtained from actual percentages reported in previous studies or by estimating the expression levels in

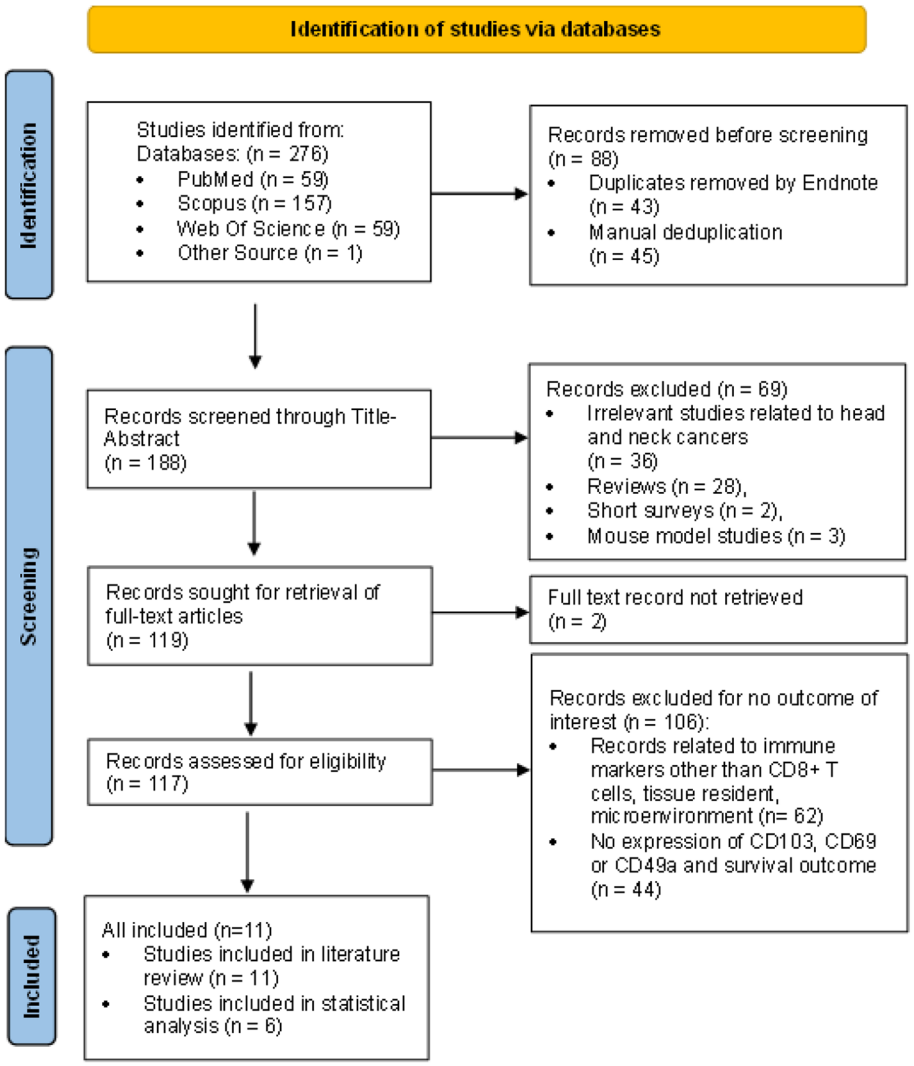

Fig. 2 Flow diagram of the selection of relevant studies included in the systematic review and meta-analysis following PRISMA 2020 guidelines

bar graphs, box plots, or scatter plots using the software ImageJ. The mean percentage of CD8 + TRM cells expression, along with standard deviation (SD), observed across different cancer types was 35.52 ± 22.27, as depicted in Fig. 4.

The potential characteristics of the included studies are consolidated in Table 3. The studies included for statistical analysis had NOS scores greater than 6 as these were considered high-quality studies after assessing the risk of bias shown in Table 4 (details provided in supplementary material).

Association between CD8 + TRM cells and survival outcome of HNSCC, and related subcategory, OSCC patients

In the current meta-analysis, six studies investigated the association between CD8 + TRM cell expression and OS in patients with HNSCC. Of these, three studies focused on OSCC, one focused on OPSCC specified HNSCC, and two included mixed or unspecified HNSCC subsites. As a result, the overall findings suggest a potential association between CD8 + TRM cells and OS in HNSCC, and the extrapolation of results to specific subsites was performed cautiously. The robustness of the evidence appears strongest for OSCC, where the majority of the studies were conducted. A high level of heterogeneity was observed ($I^2 = 88.60\%$, $P_{heterogeneity} = 0.05$) among the studies, suggesting that the effect sizes varied across them, as reflected by the differing lengths of the horizontal lines in the forest plot (Fig. 5). To account for this heterogeneity, a random-effects model with logarithmic transformation of HR was applied to stabilize the variance and normalize the data. Most of the studies reported HR < 1, indicating a lower risk of death or progression with the expression of CD8 + TRM cells in all cancer types, including HNSCC and subcategories, OSCC and OPSCC. The pooled HR was -0.72, with a 95% CI of -1.47 to + 0.02. Since the CI included 0, there was no statistically significant overall effect. However, the point estimate suggested a trend towards a reduced hazard. The reverse-transforming the overall log (HR) for interpretation of results, the transformed pooled HR was 0.49 (95% CI: 0.23 to 1.02, $p > 0.001$), indicating a strong association between CD8 + TRM T cell expression and improved overall survival in patients with OSCC, HNSCC, and OPSCC.

We concluded that CD8 + TRM T-cell expression had a protective effect in all types of cancers studied, as several studies showed significant effects, particularly those with lower HRs and narrower CIs. However, the overall effect was not statistically significant owing to heterogeneity and the inclusion of studies with less consistent findings.

Cancer Type analysis for OS after stratification to different cancer types

The log(HR) for OSCC observed in cancer type analysis was 0.00 (95% CI: -0.76—0.76, $p < 0.05$) with substantial heterogeneity ($I^2 = 92.61\%$, $P_{heterogeneity} = 0.01$); for HNSCC was -1.75 (95% CI: -3.28—-0.22, $p < 0.05$) with no heterogeneity ($I^2 = 00.00\%$, $P_{heterogeneity} = 0.52$), and for OPSCC was -1.45 (95% CI: -2.28—-0.62, $p < 0.05$) with no heterogeneity ($I^2 = 00.00\%$, $P_{heterogeneity} = 0.67$) (Fig. 6). The pooled effect for OSCC was not statistically significant, so there was no strong evidence towards a reduced hazard. The pooled effect for HNSCC and OPSCC was statistically significant, indicating a reduced hazard. The overall pooled effect, considering all cancer types, was not statistically significant ($p < 0.05$). Thus, this suggests that the effect of CD8 + TRM T cell expression varies across different types of squamous cell carcinomas of the head and neck region.

Publication bias

Egger's test was performed to assess publication bias in the current study. The funnel plot (Fig. 7) appeared to be somewhat asymmetrical, with a slight clustering of studies on the left side. Thus, we suggest the possibility of publication bias, where smaller studies with less significant results might be less likely to be published (Egger's Test z = -1.93, p-value = 0.0535). The p-value was marginally insignificant (p-value = 0.0535) (Fig. 4). This indicated some evidence of small study effects, which could be indicative of publication bias. However, the evidence is not very strong. Based on the funnel plot and Egger's test, we concluded that there was a weak suggestion of a publication bias. However, the evidence is inconclusive.

The "trim and fill" analysis is a method used to adjust for potential publication bias in meta-analyses. The observed studies showed the original pooled effect size, which was -0.723 (95% CI: -1.467–0.020) (Fig. 2). The observed and imputed studies showed a pooled effect size after accounting for missing studies. In that case, the effect size was -0.486 (95% CI: -1.190—0.219).

It was observed that the pooled effect size shifted towards a less negative value after adjusting for publication bias. Therefore, it could be suggested that the original estimate might have been biased due to missing studies. The confidence interval also widened, indicating increased uncertainty in the estimate after accounting for publication bias.

In conclusion, the "trim and fill" analysis suggests that publication bias might have influenced the original pooled effect size. However, the adjusted estimate was still not statistically significant. Thus, this signified that the effect of CD8 + TRM cell expression remained uncertain even after addressing publication bias.

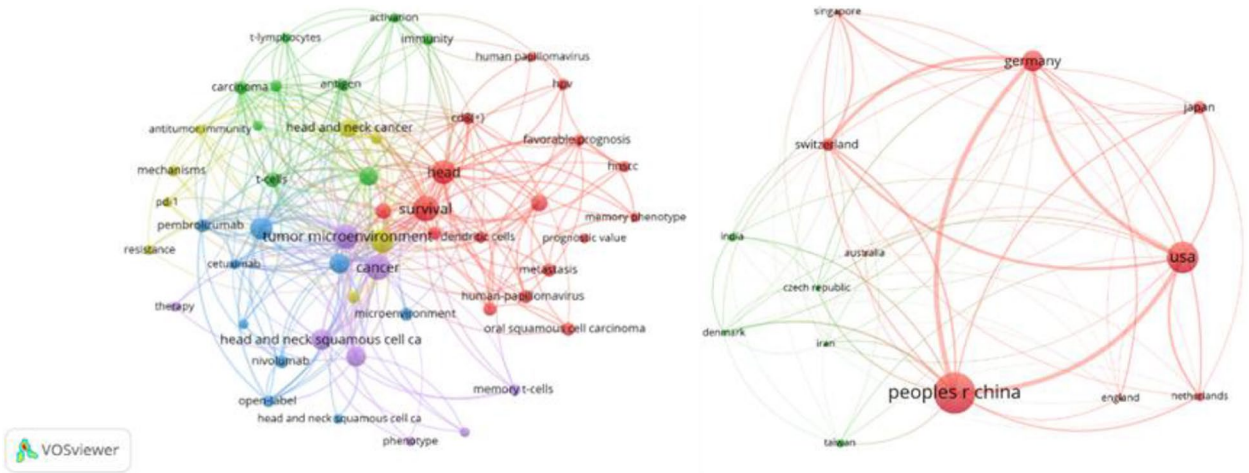

Fig. 3 Variations in geographical cluster of studies retrieved from Web of Science

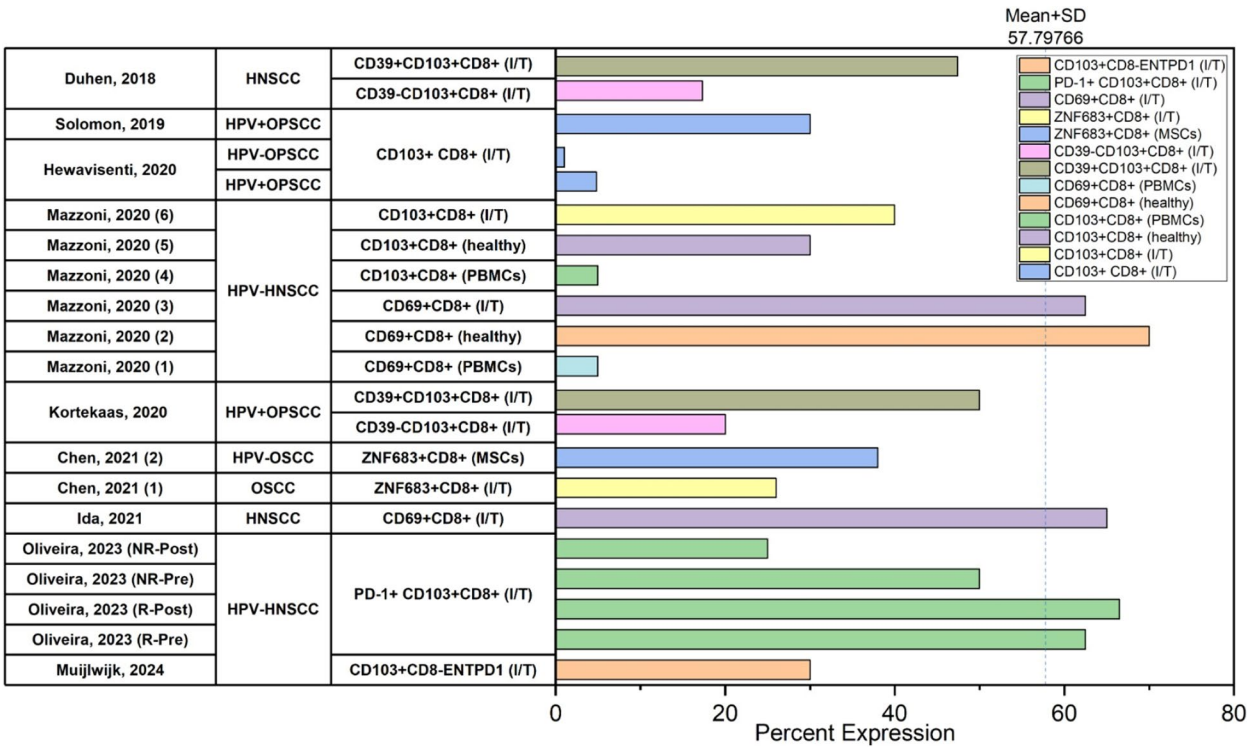

Fig. 4 The percentage expression of CD8 TRM cells across different cancer types, observed in the included studies

Discussion

This systematic review and meta-analysis primarily focused on OSCC, a recognized subtype of HNSCC, ensuring its inclusion within a broader HNSCC cohort. Additionally, some studies reported OPSCC due to shared immunological characteristics, particularly overlapping CD8 + TRM cell infiltration patterns and the expression of CD103, CD69, and CD49a. OPSCC findings were retained in the results of this study to provide a comprehensive analysis of CD8 + TRM cells in HNSCC. However, hypopharyngeal and laryngeal SCC were not included due to the absence of relevant data on CD8 + TRM expression and survival outcomes in the studies meeting our inclusion criteria.

Since OSCC and OPSCC are subsites of HNSCC, the studies included in this meta-analysis reported survival

Table 3 Consolidated characteristics of included studies

Author	Tumor specific subsites	HPV status	Clinical stages	Study design	Tissue specimens	Comparative specimen	Diagnostic Methods
Muijlwijk, 2024 [38]	HNSCC: oral cavity, hypopharynx, oropharynx	±	All TNM stages	Observational, descriptive	Intratumoural ($n=76$)	Tumour adjacent mucosal tissue ($n=25$)	Flow cytometry, scRNA-seq
Oliveira, 2023 [39]	HNSCC: oral cavity, hypopharynx,	-	TNM stages III and IV	Phase II clinical trial	Preintervention Intratumoural cohort 1, 2 ($n=13$),	Postintervention Intratumoural cohort 2 ($n=7$)	Multiplexed IHC, scRNA-seq, TCR-seq
Ida, 2021 [40]	HNSCC: oral cavity, hypopharynx, oropharynx	±	All TNM stages	Retrospective, observational	Intratumoural TCGA dataset ($n=520$)	PBMCs ($n=60$)	Flow cytometry, scRNA-seq
Chen, 2021 [41]	OSCC	NR	Stages II, III and IV	Experimental, observational	Intratumoural ($n=3$)	Tumour adjacent (non-malignant) mucosal tissue ($n=3$)	scRNA- seq
Kortekaas, 2020 [42]	OPSCC	+	NR	Experimental, in vitro	Intratumoural ($n=32$)	PBMCs	Flow cytometry, scRNA-seq, Functional assay
Mazzoni, 2020 [43]	HNSCC, unspecified subsites	-	NR	Experimental, observational	Intratumoural/ MSCs ($n=10$)	Healthy mucosa/ PBMCs	IHC, Flow cytometry, Transcriptome analysis
Hewavisenti, 2020 [44]	OPSCC	±	All TNM stages	Retrospective, observational	HPV + Intratumoural TCGA dataset ($n=35$)	HPV- Intratumoural TCGA dataset ($n=27$)	Multiplex IHC,
Solomon, 2019 [45]	OPSCC	+	All TNM stages	Retrospective, Observational: validation Study	Intratumoural prospective cohort ($n=189$)	Intratumoural retrospective cohort ($n=177$)	multispectral IHC, gene expression profiling
Xiao, 2019 [46]	OSCC	+	All TNM stages	Retrospective, Observational	Intratumoural / Stromal tissues ($n=44$)	PBMCs / fresh TILs	MxIHC, flow cytometry, pan-keratin staining
Duhen, 2018 [47]	HNSCC, unspecified subsites	±	All TNM stages	Experimental, Descriptive	Intratumoural tissues / metastatic LN ($n=65$)	PBMCs	Flow cytometry, Genetic profiling
Vora, 2017 [48]	OSCC	±	All TNM stages	Retrospective, observational	Intratumoural TCGA dataset ($n=546$)	Intratumoural Oral Chip data ($n=166$)	Genetic profiling

Abbreviations: HNSCC Head and neck squamous cell carcinoma, *OSCC* Oral squamous cell carcinoma, *OPSCC* Oropharyngeal squamous cell carcinoma, *CxCa* Cervical Carcinoma, *VSCC* Vesicular squamous cell carcinoma, *HPV* Human papilloma virus, *+ sign* expressed,—*sign* not expressed, *NR* not reported, *TCGA* The Cancer Genome Atlas, *MSCs* Mesenchymal stromal cells, *PBMCs* peripheral blood mononuclear cells, *Sc-RNA-seq* single cell RNA sequencing, *TCR-seq* T cell receptor sequencing, *MxIHC* multiplexed Immunohistochemistry, *IHC* Immunohistochemistry

Table 4 Consolidated Knowledge of Tissue Resident memory of CD8 and related Immune markers from Included Studies

Author, year	Tissue Resident Markers	Related Immune Factors	Outcome of Interest for CD8 + TRM cells	Key Findings	Total NOS Score
Muijlwijk, 2024 [38]	CD103	Trm: ENTPD1(CD39), TF: ZNF683; ID1; TOX; HOPX, Chemokines: CXCL3; CCL3; CCL4, EM: GZMH, IFNG, PRF1, ICM: LAG-3; HAVCR2(TIM-3); TIGIT; LAYN	% expression of CD103 + ENTPD1-CD8 + ; estimated	Higher CD8 + T cells in mucosal tissues of TME than tumour tissues	9/9
Oliveira, 2023 [39]	CD103, CD69, CD49a	Trm: ENTPD1 (CD39), TF: ZNF683 (CD103), Chemokines: CXCL13, EM: GZMH; GZMK; SLAMF7; EOMES, ICM: PDCD1; HAVCR2, CTLA4, TIGIT, TOX	% expression of CD103 + PD-1 + CD8 + ; estimated	High density of CD8 + TRM cells in pre/post-intervention tumour tissues, correlated with prognosis	9/9
Ida, 2021 [40]	CD8, CD69	EM: INFG; GZMB, ICM: PD-1; LAG-3; TIM-3; CTLA4; TIGIT; ICOS	OS, % expression of CD69 + CD8 + ; estimated	Favorable prognosis and proinflammatory stimulation in TME	9/9
Chen, 2021 [41]	CD8, ZNF683	TF: ZNF683, EM: GNLY; PRF1; GZMB; GZMH; GZMA, ICM: LAG3; CTLA4; HAVCR2 (TIM3), Immune-related pathways: antigen binding, chemokine and cytokine receptor binding and activity; MHC binding; response to INFG; TCR signalling	OS, % expression of CD8 TRM; estimated	Higher density of CD8 TRM cells in tumour tissue suggested immediate localized stimulation and clonal expansion for tumour suppression	8/9
Kortekaas, 2020 [42]	CD8, CD103 (ITGAE) and CD49a (ITGA1)	Trm: CD39, Chemokine: CXCL13, ICM: PDCD1 (PD-1); LAG-3, EM: IFNg; GNLY; GZMB; PRF1	% expression of CD8 + CD39 + CD103 + , CD8 + CD39-CD103 + ; estimated	Infiltration of CD103 TRM expressed predominantly on surface of CD8 + nonregulatory T cells compared to CD8 Treg and CD4 effector memory population among TIL	9/9
Mazzoni, 2020 [43]	CD8, CD103, CD69, PD-1,	IL-7, IL-15, IL-15ra, Notch ligands, VCAM1 (CD106)	% expression of CD69 + CD103 + CD8 + ; estimated	MSCs facilitate survival and mediate tissue residency markers through VCAM1-depnedant pathway	8/9
Hewavisenti 2020 [44]	CD8, CD103, CD69	NR	OS, % expression of CD103 + CD8 + TRM cells; Actual	High intra-tumoral and stromal density of CD103 + CD8 + TRM cells was associated with better survival irrespective of HPV status	9/9
Solomon, 2019 [45]	CD8, CD103, CD69	Chemokines; CCL3; CCL4; CCR5 ICM: LAG3; HAVCR2/TIM3 EM: PRF1; GZMA; GZMH	OS, PFS, % expression of CD103 + CD8 + TRM cells; cut point,30%	19.8% Intratumoural abundance of CD103 + CD8 + TRM cells observed in cohort 1 and 20.4% in cohort 2	9/9
Xiao, 2019 [46]	CD8, CD103, CD69	CD45RO, PD-1, CD11c encoding dendritic cell in tumour stroma	OS of CD103 + CD8 + TRM cells; median cut point, P = 0.0231	Stroma was enriched with CD103 + CD8 + TILs than CD103 + CD11c + TILs and showed prognostic significance more than Intratumoural tissues	9/9
Duhen, 2018 [47]	CD8, CD103, CD69	TGF-β, ICM: CD39; PDCD1 (PD-1); CTL4 (CTLA-4); HAVCR2 (TIM-3), Downregulatory marker: KLF2; SELL (CD62L); S1PR1, EM: INF-γ; GZMB; TNF-α	OS, expression of CD39 + CD103 + CD8 + , CD39-CD103 + CD8 + ; actual	Higher expression of double positive CD8 TRM cells significantly decreased the risk of death in patients of HPV ± HNSCC	9/9

Table 4 (continued)

Author, year	Tissue Resident Markers	Related Immune Factors	Outcome of Interest for CD8 + TRM cells	Key Findings	Total NOS Score
Vora, 2017 [48]	cytotoxic CD8	Genetic profiling of activated memory T cells; follicular helper cells; regulatory T cells	OS associated with cytotoxic CD8 T cells	Higher concentrations of cytotoxic CD8 + T cells linked to better prognosis	9/9

Abbreviations: TRM tissue resident memory, *Trm* tumour reactive marker, *ICM* immune checkpoint molecules (exhaustion/activation), () sign encoded molecules, *EM* effector molecules, *TF* transcription factor, *OS* overall survival, *% sign* proportion of expressions. + *sign* expressed,—*sign* not expressed, *NR* not reported, *IL* interleukin

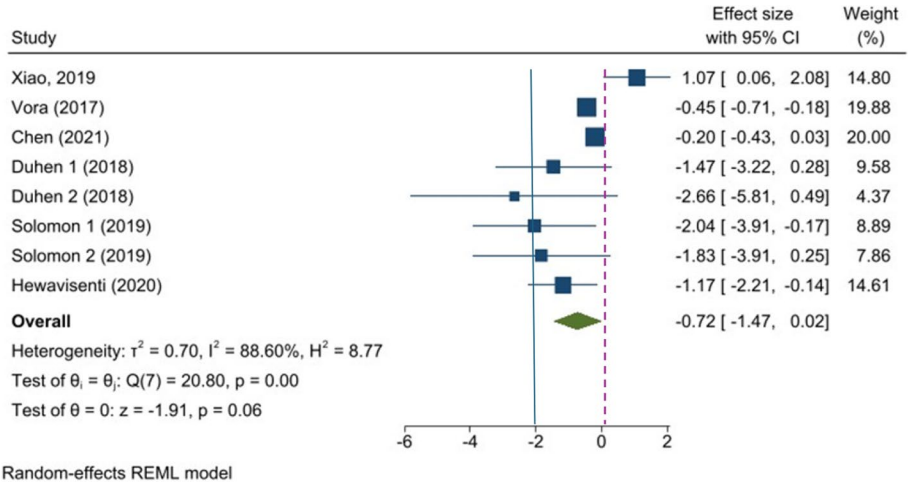

Fig. 5 Forest plot describing the association between CD8 + TRM cells and OS in HNSCC, OSCC and OPSCC

outcomes either for HNSCC as a whole or separately for its subtypes, OSCC and OPSCC. HR values were presented as reported in the original studies rather than directly compared across groups to maintain consistency. Evidence was gathered to highlight subsite-specific findings, the strength of the evidence for OSCC, and the potential limitations. PubMed, Web of Science, and Scopus databases were surveyed for this observation and analysis.

The study results reveal that this phenotypic profile has not been found to be mutually essential or mutually exclusive in tumors and MSCs of the TME. We observed co-expression of CD103 and CD8 markers in eight studies, CD69 and CD8 markers in five studies, and CD49a and CD8 markers in two studies. We also observed mutually expressed CD103 and CD49a phenotypic markers on the surface of CD8 + T lymphocytes [39, 42]. As these are integrin receptors, it is documented in previous literature that they mutually play a potential role in epithelial adhesion in tumor and stromal tissues of various cancer types [49]. We identified CD8 TRM cells targeting ZNF683 (HOBIT) among CD8 + T-cell clusters. It has been observed in previous studies that ZNF683 is a distinctive transcription factor that regulates CD103 expression and is targeted for isolation of TRM cells from cytotoxic T cell populations. We found our findings consistent with its prognostic role in lung cancer [50].

In the current study, we also identified genetic signatures consistent with the known functional characteristics of TRM, which include elevated cytokine production and cytotoxic activity such as transcription factor ZNF683; effector molecules IFNg, GNLY, GZMB, and PRF1; immune checkpoint molecules/exhaustion markers PD-1, CTLA4, HAVCR2 (TIM3), and LAG3; and downregulated egress markers KLF2, SELL (CD62L), and S1PR1 to prevent recirculation of TRM cells. Thus, their role has been discovered in immune checkpoint blockade and immunotherapy, inhibiting the progression and recurrence of head and neck cancers.

The study results in the forest plot (Fig. 5) show the pooled HR < 1 predicting the protective effect and demonstrate studies with reliable outcomes in the overall meta-analysis. These influential studies predicted the probability of adequate sample size, better study design, or precise estimates of CD8 + TRM expression and survival rates with narrow confidence intervals. Hence, our analysis showed that CD8 + TRM cells linked to phenotypic markers of CD103, CD69, and CD49a are indicative of better overall survival due to immune response. Moreover, our findings are consistent with the evidence of a high increased abundance of TRM phenotypic markers leading to immune-competent microenvironment in NSCLC with better prognosis and survival [31]. We found an increased risk for events like tumor progression, recurrence, or mortality in the studies related to OSCC, as point estimates (blue squares) were lying above the null line. It can be due to variations in study characteristics, inclusion of advanced stages of OSCC, or genetic variations. However, our analysis found inconclusive evidence of increased or decreased risk of adverse outcomes in studies conducted on patients with HNSCC. Therefore, further research targeting phenotypic residency markers of CD103, CD69, and CD49a linked to CD8 + T cells is recommended to clearly define the function of TRM in the outcome of HNSCC and its subcategory, OSCC. There may be a need to include larger trials, advanced molecular techniques, and genetic profiling. However, we observed better prognosis and survival in

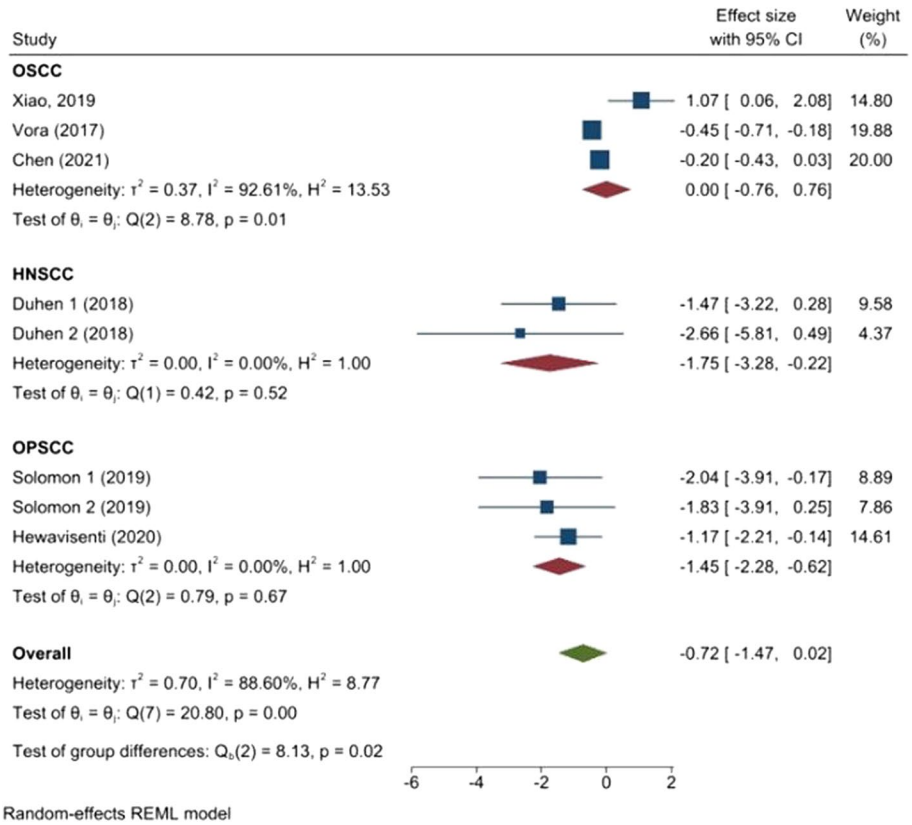

Fig. 6 Forest plot of OS in association with various types of head and neck cancers

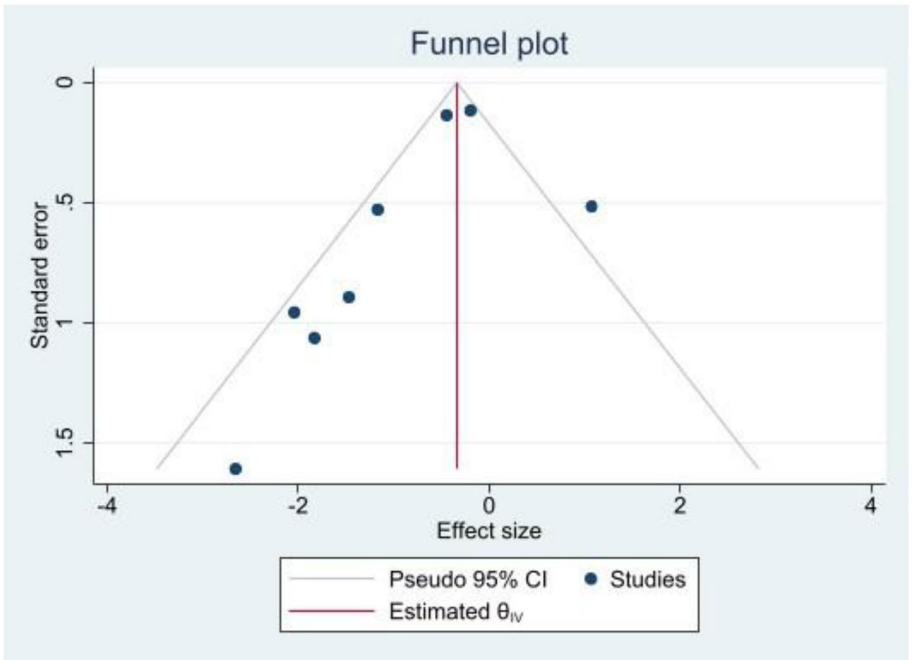

Fig. 7 Publication bias and trim and fill analysis of the enrolled studies

patients with OPSCC correlated with phenotypic markers of CD8 + TRM cells [40].

Conclusively, these key findings of our study highlight the significance of CD103, CD69, and CD49a immunophenotypic expression and CD8 + TRM cells in determining prognosis and survival in cancer patients. Enhancing TRM cell function or increasing their presence in the TME, particularly by upregulating markers such as ZNF683, GNLY, PRF1, GZMB, GZMH, GZMA, CD103, and CD69, could improve patient outcomes in HNSCC and OSCC. Targeting MSCs-TRM interactions, especially through expansion of TGF-β and survival factors; IL-7, IL-15, and regulatory mechanisms of notch signaling and VCAM1 pathways, could enhance antitumour immunity [43].

The key limitation of this study was the significant heterogeneity among the included studies. This heterogeneity may stem from differences in study design, sample size, phenotypic characterization, or tumor staging. Another limitation of the study is the lack of HPV stratification in OPSCC cases, as most included studies did not differentiate between HPV-positive and HPV-negative OPSCC. Given the distinct immunological characteristics of these subtypes, future research should focus on stratified analyses to determine the prognostic impact of CD8 + TRM cells in HPV-positive versus HPV-negative OPSCC. Therefore, it is recommended that the results should be interpreted cautiously due to the absence of HPV-specific stratification in our included studies. Further studies are required to establish surface markers of CD8 + TRM cells for their specific identification.

This study explored the immune response and phenotypic markers of CD8 TRM cells against head and neck cancers, particularly OSCC, for the first time for identification in the local TME and immuno-modulating therapies. We also underscored the expression levels of immunophenotypic biomarkers of TRM cells: CD8, CD103, CD69, CD49a, ZNF683, CD39, and PD-1 in the TME of HNSCC, particularly OSCC. Furthermore, we analyzed the research papers reporting the clinical examination of the patients for site and type of the tumors, pathological findings, staging and scoring of tumors, IHC staining, and expression patterns following the REMARK guidelines. These study parameters could help us in future research to determine the relationship between phenotypic markers and their genetic signatures in predictive, prognostic, and therapeutic modulations.

Abbreviations

HNSCC	Head and neck squamous cell carcinoma
OSCC	Oral squamous cell carcinoma
OPSCC	Oropharyngeal squamous cell carcinoma
TRM	Tissue-resident memory T lymphocyte cells
TILs	Tumor-infiltrating lymphocytes
TME	Tumor microenvironment
WOS	Web of Science
NOS	Newcastle–Ottawa Scale
REMARK	REporting recommendations for tumor MARKer prognostic studies
OS	Overall survival
HR	Hazard ratios
CI	Confidence interval
SD	Standard deviation

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
AA, MFB, SA, MW, JS, KA, and WAF have made substantial contributions equally to the conception, design, data analysis, and interpretation of data and have drafted the work. All authors reviewed the manuscript.

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Competing interests
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